TEXTBOOK OF MEDICINE

R S VASAN SUDHA SESHADRI

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Orient Longman

Orient Longman Limited

Registered Office
3-6-272 Himayatnagar, Hyderabad 500 029 (A.P), India

Other Offices
Bangalore/Bhopal/Bhubaneshwar/Calcutta/Chandigarh/Chennai
Ernakulam/Guwahati/Hyderabad/Jaipur
Lucknow/Mumbai/New Delhi/Patna

© Orient Longman Limited 1998

First Published 1998
Reprinted 1998

ISBN 81 250 1599 0

Cover design by
Deepa Kamath

Typeset by
Venture Graphics
Chetput, Chennai 600 034

Printed in India by offset at
Indcom Press
West Mambalam, Chennai 600 033

Published by
Orient Longman Ltd
160 Anna Salai, Chennai 600 002

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Preface

The medical student faces a challenging task in India today and in other countries of the South. The health care priorities here are different from those of the developed countries and the student is expected to acquire the necessary knowledge and skills to deal with problems peculiar to the country. In addition, as these countries make the transition from 'developing' to 'developed' nations, they are faced with a growing burden of noncommunicable diseases and the student is expected to learn about these conditions as well. Furthermore, with giant strides in medical research, with the virtual flood of scientific information, and the burgeoning influence of technology, the medical student needs to keep pace with recent developments in the medical field. Developments which seem of theoretical relevance today are likely to assume practical importance tomorrow.

The task of writing a textbook to cater to these diverse needs was daunting. We have undertaken this ambitious task in the hope of 'lighting a candle'. We have both been fortunate to have been taught by excellent teachers and to have worked at institutions where teaching has been accorded the highest priority. We hoped to create a comprehensive textbook of medicine primarily for medical undergraduates, written in simple English, building on the foundations of preclinical years and focusing on conditions in India.

We have tried to present the basic information necessary for providing a high quality of patient care. To make it user-friendly, the book has been illustrated profusely so that information may be more easily assimilated. Short summaries which complement the text and facilitate quick revision have been provided. We have tried to blend a 'syndromic' approach with a 'disease-based' approach within the same text. We have kept our language simple and used numerous footnotes to explain difficult terms which needed to be introduced.

Our efforts to write a more comprehensive book have been constrained by the limitations of available space; a book of over 1400 pages is formidable for even a spirited young medical student. We have therefore intentionally omitted sections on dermatology, medical oncology and critical care medicine, for which the student is urged to read additional books.

Books of this kind are printed but not complete. Indeed, we see the book as a project in evolution which we hope will change its form, shape, and structure to accommodate criticism, suggestions, emerging needs and information. We encourage the readers to communicate their views to us as we view them as our partners in this project and the ultimate arbiters of its worth.

R. S. Vasan
Sudha Seshadri

To the memory of Chitra and Seshadri,
and to all the 'music makers' of the world

We are the music makers and we are the dreamers of dreams
Wandering by lone sea-breakers and sitting by desolate streams
World losers and world forsakers on whom the pale moon gleams
Yet we are movers and shakers of the world forever it seems...

ARTHUR WILLIAM O'SHAUGHNESSY

Authors' Acknowledgements

We would like to thank the many people who have at different stages played a pivotal role in making this book possible. We must first thank Usha Aroor, our editor, for her faith in our ability to write such a book. But for her vision of the book, we may have never embarked on the project. At times when we were on the verge of wilting under the tremendous strain of attempting such a book, she never failed to provide the vital support that made the difference between a completed book and an abandoned project. It would be appropriate in this context to thank Dr Akash Rose, who enabled our initial contact with Usha Aroor, and Rohini Herbert the initial editor, whose talent and enormous efforts nurtured the book in its early stages. Padmaja Anant, the subsequent and final editor, has since groomed, nourished and developed the infant to its current presentable childhood. In this arduous process, she has put in a tremendous amount of effort and tolerated our numerous procrastinations of deadlines with admirable restraint and patience.

We thank the National Book Trust of India for subsidising the book, and Professors P. N. Tandon and O. P. Ghai for encouraging us to apply for the subsidy.

We have been assisted by Dr Indumathy Santhanam, Dr Samir Malkani, Dr Jagat Narula, Dr Richard Haas, Dr K. Suresh and Dr Hillol Kanti Pal in writing some sections of this book. They have brought to their writing enthusiasm, insight and elegant expression. They have truly salvaged the project at several stages and we owe them special thanks. We have been fortunate to enjoy their partnership in completing our dream.

We also wish to acknowledge the steadfast moral support of all near and dear friends and relatives, and to mention just a few: Suresh, Mummyji and Daddyji, Professor Rajan Tandon, Jagatji, Perrips and Bama. We couldn't have done it without you! To our many patients and our teachers who have taught us more than any book, text or journal could, we owe whatever practical wisdom we have.

This book is inspired by our daughter Aditi, who despite being less than eight years old at the time, bore with the gestation period of the book with admirable patience and provided frequent creative suggestions. She has regarded this book as a family team effort and has contributed in great measure to its seen and unseen parts.

Finally we thank God for our health, for the great experience and that it is done at last!

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Contributors

The authors owe their sincere thanks to the following friends and colleagues for their contributions to the book:

Indumathy Santhanam D.Ch. M.D. (Pediatrics)
Disorders of the Hematopoietic System (Chapter 15)

Samir Malkani M.D. D.N.B. (Endocrinology) M.R.C.P. (UK)
Diseases of the thyroid gland (Chapter 16.5)
Diseases of the parathyroid glands (Chapter 16.6)
Diseases of the adrenal gland (Chapter 16.7)
Diabetes mellitus (Chapter 16.8)
Disorders of sexual differentiation (Chapter 16.9)
Management of diabetic ketoacidosis (Chapter 16.11)

K Suresh M.R.C.P. (UK)
Neuroendocrine physiology and disorders of the pituitary gland (Chapter 16.4)

Richard Haas M.D. F.A.C.E.
Approach to a patient with hypoglycemia (Chapter 16.8)
Approach to a patient with gynecomastia (Chapter 16.2)

Jagat Narula M.D. D.M. (Cardiology) Ph.D. F.A.C.C.
Rheumatic fever (Chapter 12.8)

Hillol Kanti Pal M.Ch. (Neurosurgery)
Head injury (Chapter 9.16)

Acknowledgements
The authors and publishers gratefully acknowledge the sources of figures and tables in the book as follows:

Wyngaarden J B and Smith L H (ed) *Cecil's Textbook of Medicine* 1988. 18th edition. W B Saunders, Philadelphia Tables 12.2, 15.11, 15.24; *Arch Internal Medicine* 1972, Fig 13.1; *Hospital Medicine* 1984 (Figs 14.9, 14.16, 14.17) 1985 (Fig 11.4) 1986 (Fig 14.22) 1987 (Figs 14.6, 17.7) 1988 (Figs 17.10, 17.11) 1990 (Fig 12.71) 1991 (Fig 11.14); *Journal of Applied Medicine* 1987, Fig 11.6; *British Medical Bulletin* 1987, Fig 17.4; John Axford *Medicine* 1996. 1st edition. Blackwell Scientific, UK Table 17.1; *British Medical Journal* 1989 (Figs 3.1, 3.8, 3.9a,b, 3.10, 3.11, 3.12, 3.16b) 1993 (Table 11.10, Respiratory emergency 1); *Hospital Practice* 1988 (Figs 3.14, 3.15, 14.21a,b); *American Journal of Medical Sciences* 1986 (Fig 3.19) 1990 (Fig 3.18); *Journal of Infectious Diseases* 1982, Fig 8.8; Stein J H (ed) *Internal Medicine* 1990. 3rd edition. Little Brown, USA Fig 8.6; Kibukamusoke J W *Tropical Nephrology* 1984. Citforge Pty Ltd, Canberra Fig 14.24; James P Isbister and D Harmening Pittiglio *Clinical Hematology: A Problem Oriented Approach* 1988. Williams and Wilkins, USA (Figs 12.72, 15.4, 15.9, 15.10, 15.12, 15.20 and Tables 15.3, 15.5, 15.7); West J B *Respiratory Physiology—The Essentials* 1983. 2nd edition. Williams and Wilkins, USA Fig 11.2; *Bulletin of WHO* 1993 (Fig 12.68); Jay P Sanford *Guide to Antimicrobial Therapy* 1992, 1993 (Tables 8.15, 8.25, 12.28, 12.29); *Journal of the American Medical Association* 1990 (Tables 12.28, 12.29); *International Journal of Cardiology* 1994 Table 12.25; *Disease a Month* June 1992 (Fig 12.25); *Southern Medical Journal* 1995 Fig 12.34; *British Hematology* 1981 Table 15.26; *Cancer Research* 1971 Table 15.28; *Polycythemia Vera Study Group*, Table 15.32; *Cancer* 1975, Table 15.35; Framingham Heart Study, USA, used with the permission of P W F Wilson, Fig 16.26; *Physiology, NMS Series*, Fig 16.1 Appendix B Biochemical values: *New England Journal of Medicine* 1986; 314: 39–49 and 1986; 315: 1606

1

Medicine as an Art and a Science

MEDICINE AS AN ART

The practice of medicine in its broadest sense includes the whole relationship of the physician with his patient. It is an art, based to an increasing extent, on the medical sciences, but comprising much that still remains outside the realm of any science. The ***art*** *of medicine and the* ***science*** *of medicine are not antagonistic but supplementary to each other. There is no more contradiction between the science of medicine and the art of medicine than between the science of aeronautics and the art of flying.*

The treatment of the disease may be entirely impersonal, the care of a patient must be completely personal.

What is spoken of as a "clinical picture" is not just a photograph of a man sick in bed; it is an impressionistic painting of the patient surrounded by his home, his work, his relations, his friends, his joys, sorrows, hopes and fears.

Care of the Patient
Francis Peabody 1927

The last decade has witnessed dramatic changes in the field of medicine: new diseases, newer and more effective medicines and vaccines, and, of course, rapid technological advances. In such an atmosphere surcharged with the excitement of scientific breakthroughs, one would expect the physician to be respected all the more. It is regrettable that today the 'doctor-patient' relationship has been eroded considerably. A substantial proportion of patients believe that doctors 'do not explain things to them', 'do not spend enough time with them' and 'are more interested in money'.

This erosion of credibility, brought about by increasing commercialism and entrepreneurial activity, reflects the failure of the physician to balance the *science* of medicine with the *art* of medicine.

The art of medicine implies that the secret of good care *of* the patient is in caring *for* the patient. It entails the qualities of humanism, diligence, honesty, altruism and ethical behaviour.

Humanism is the attitude of giving primary importance to human interest, values and dignity. It is the skill required to handle demanding interpersonal situations involving patients and their families, the ability to be courteous to the patient and her family at all times, sensitivity to their need for information, contact and encouragement and finally, respect for their privacy. Physicians must also respect the patients' choices regarding their care. Poverty, illiteracy and ignorance in the patient and his relatives are not an adequate excuse for the physician to be the sole decision-maker. Physicians must encourage rather than discourage questions, answering them as simply and clearly as possible. They should be receptive to the patient's views, however absurd they may sound, and dispel their anxiety with explanations and, if necessary, gentle repeated reassurances.

Rather than abjectly obey orders, patients should be encouraged to take charge of their health under the doctor's guidance. To this end,

the physician should consciously try to remain approachable and not seem distant and forbidding. Care must be taken not to destroy the hope within the patient. It is also a worthwhile practice to have the patient repeat the doctor's instructions to make sure that he has fully understood them. The physician must also recognise the importance of the non-verbal skills in communication. Facial expressions and the degree of animation in conversation may indicate to the patient how involved the physician is. Physicians must not forget the importance of simple gestures such as sitting down while talking to the patient or a simple gentle touch that may serve to establish a care-giving bond.

Diligence and honesty demand a sense of commitment to one's duty and putting nothing but the best that one has into the task of patient care.

A certain amount of altruism defined as unselfish concern for or devotion to the welfare of others is an intrinsic part of medicine. A physician must place the welfare of the patient above his other social, financial or academic self-interest.

Ethical behaviour requires that the doctor maintains confidentiality, obtains informed consent, retains accountability and shows a respect for human rights in dealings with patients.

The science of medicine must be dovetailed with the art of medicine for both the physician and the patient to get the best out of each other.

MEDICINE AS A SCIENCE

The scientific method is well-known to all students of science and it applies to medicine as well. It involves the generation of a 'tentative hypothesis', 'the setting up of an experiment' and the analysis of results obtained from the experiment to see whether the hypothesis is supported or refuted. Clinical medicine involves the use of observational skills to obtain *information* regarding the patient's disease. The information obtained from several sources (history, examination, laboratory) is *organised* and *synthesised* to yield a set of diagnostic possibilities (differential diagnosis). Clinical skills are then used again in selecting the 'tentative diagnosis' and making further observations or tests to support or refute the tentative diagnosis. If the diagnosis is refuted, another one is tested—a cyclical process referred to as *iterative hypothesis testing*. If the diagnosis is established, clinical judgement is used to decide what form of management is of greatest benefit to the patient at the least risk and cost. This clinical decision-making is discussed in detail in the next chapter.

The process of clinical information collection must also bear scientific scrutiny. The physician must be aware of the accuracy, the precision, the variance, the validity, the sensitivity and the specificity of the information in order to be truly scientific. All these terms must be clearly defined and understood. By *accuracy* we mean how closely the given information reflects the true state. Thus accuracy of a specific method of hemoglobin estimation is assessed by analysing a sample with a known authentic hemoglobin value (the gold standard) by the given method, and looking for the extent of agreement between the observed and the true value. *Precision* refers to the reproducibility of a piece of clinical information as measured by the variability in the results when the observation is repeated. Clearly, information which is precise need not be accurate.[1] *Variability* in the observations may occur when the same person repeats the observation (*intraobserver* variability) or when repeated by another observer (*interobserver* variability). For instance, we can measure the size of an enlarged liver by the number of finger breadths below the costal margin that the liver is palpable; however, the size may vary from

[1] For instance, a reproducible (precise) blood pressure in a hypertensive patient need not reflect the true intraarterial blood pressure (that is, it may be inaccurate).

observer to observer, depending on the breadth of the observer's finger or on the phase of respiration the measurement is made in. The *span* of the liver (measured from the percussable upper border to the palpable lower border) would be more accurate, precise and less variable.

The presence or absence of certain clinical findings leads the clinician to draw certain inferences regarding the condition of the patient. The *sensitivity* of a test is its ability to detect true positives. The *specificity* of a test helps us to know whether the disease can be excluded if the test were negative, that is, the ability to detect true negatives. Two other terms the physician must be aware of are the *positive predictive value* and *negative predictive value* of a test. The positive predictive value of a test tells the clinician about the probability of the disease in a patient with a positive test. The physician must realise that a test (with given sensitivity and specificity) may have a variable predictive value in different groups of patients depending on the prevalence of disease in the given groups.[1] Thus, mildly elevated serum transaminase levels may be 'true positives' in the subgroup of patients recovering from viral hepatitis. The same values in an asymptomatic person (obtained as part of a routine screening) are likely to be 'false positives' (Fig 1.1) .

	Disease State (gold standard)	
Given+	a (true positive)	+ b (false positive)
Test −	c (false negative)	− d (true negative)

$$\text{Specificity} = \frac{d}{b+d}$$

$$\text{Sensitivity} = \frac{a}{a+c}$$

$$\text{Positive predictive value} = \frac{a}{a+b}$$

$$\text{Negative predictive value} = \frac{d}{c+d}$$

$$\text{Overall accuracy} = \frac{a+d}{a+b+c+d}$$

Fig 1.1 Definition of some commonly used terms

Thus, the physician has to be scientific in obtaining information, in interpreting the information as well as in acting on the clinical information.

[1] This idea has been quantified as 'Bayes theorem' which states that the 'post hoc' probability of a given disease depends on the pretest probability of having the disease (estimated by the prevalence of the disease).

KEY CONCEPTS

- Care *of* the patient is in caring *for* the patient.
- The *art* of medicine is the combination of medical information and intuition with good judgement. It involves guiding patients through an illness: listening to and understanding their problems with compassion, obtaining informed consent prior to testing, keeping patients informed about test results, addressing their anxieties at every stage and conducting oneself with a sense of accountability.
- The *science* of medicine is the combination of obtaining clinical data, formulating and testing hypotheses with inductive reasoning. It involves the integration of medical knowledge (with history, examination, laboratory and imaging tests) with current practice guidelines, assessment of outcomes (with objective and subjective means) and the monitoring of cost-effectiveness of the treatment modalities instituted.
- The *sensitivity* of a diagnostic test is its ability to detect true positives, the *specificity* is its ability to detect true negatives. *Precision* refers to repeatability whereas accuracy refers to the ability to detect the true state correctly.

2

Decision-making in Clinical Medicine

Good clinical judgement requires optimal decision-making. The average physician encounters many 'routine' clinical problems generating solutions which are 'established' practices. On the other hand, there are clinical situations which constitute problems even to the experienced physician. These may be situations with diagnostic or therapeutic uncertainty and situations where the optimal sequencing of procedures is not clear.

Decision analysis involves the break-up of a complex problem into a series of smaller ones and combining all the solutions by structuring a model of the decisions, usually in the form of a *decision tree*. The first step in such a process is to design a tree by defining the various options (*decisions*) available to the patient. These are represented as circular nodes on the decision tree. The next step is to define the various *outcomes* that may result from each decision, the outcomes being depicted as rectangular nodes. The likelihood of each outcome is defined in terms of a *probability,* ranging from 0 to 1. Such a likelihood is obtained from literature based on the natural history and treatment of a disease, with adjustments being made for individual patient-related factors. In the absence of data from clinical trials, the subjective judgements of experts can be used for the same purpose. The next step is to assign a numerical value, called a *utility*, to each outcome. The values reflect the relative preference for each outcome, a perfect outcome being assigned a utility value of 1 and the worst outcome (say, death) a value of 0. In the next step the decision tree is traced to its origin by multiplying the probability of each outcome with its utility value and adding the products for all branches of the node. Then the preferred strategy is the branch yielding the maximum expected utility at a node. Lastly, *sensitivity analysis* is performed by varying one or several of the probabilities assumed in the analysis and seeing how sensitive a decision is to a change in probability. If a decision is unaffected by reasonable changes in the probabilities of various outcomes, it can be recommended with greater confidence.

Analysis of a case

Consider the example of a marker symptomatic sixty-year-old lady (Fig 2.1) with critical calcific aortic stenosis who is also detected to have a resectable colonic malignancy. The options available to the physician are twofold: 1) to resect the diseased colon first and then replace the aortic valve at a later date, or 2) first replace the aortic valve and then perform the colonic resection. If colonic surgery is performed first, the patient stands the risk of intraoperative hemodynamic collapse due to the obstructive aortic valve. If aortic valve surgery is first performed, in the unavoidable interveni period, the hitherto localised colonic malignan may metastasise. The clinician then has to calculate the maximum expected utility (usually in terms of *quality-adjusted life expectancy*) of either strategy. For this the following kinds of information must be made available to t

clinician: 1) What is the probability of occurrence of intraoperative hemodynamic collapse in a patient with critical aortic stenosis undergoing major abdominal surgery? 2) What is the probability of survival of a patient with critical aortic stenosis who develops hemodynamic collapse? 3) What is the operative mortality for critical aortic stenosis? 4) What is the risk of developing mestastases in a patient with a resectable colonic malignancy over a short waiting period (after the cardiac surgery)? 5) What is the life expectancy of a patient with a colonic malignancy and metastases? 6) What is the operative mortality of colonic resection performed for a colonic malignancy? The physician must select that strategy which has a maximum expected utility.

Decision analysis—a critique

While the excellent assistance that decision analysis may provide the physician is obvious, it must be remembered that such an analysis is fraught with problems. Not only is the expertise in using the method limited but the process too is time-consuming. Further, the decision tree itself is a model of simplified probabilities which may be fallacious in real-life situations.

On the other hand, decision analysis does force one to consider all patient outcomes, bringing forth in the process all the assumptions about a clinical problem. With further advances in methodologic research it may help us to learn quantitative problem solving, that is, help one to dissect threadbare the day-to-day clinical decisions that form the alpha-omega of clinical medicine.

Doctor–patient disagreement

It would not be unusual to have the patient's preferences differing from the physician's (the latter derived from the decision analysis). This may stem from inadequate patient information leading to fears related to a therapeutic option or it may be due to a difference in perception of 'qualities' of a life (the patient may prize some characteristics of life more). The final decision should be made by a consensus between a well-informed patient and an understanding, perceptive physician, after a detailed discussion on the various outcomes.

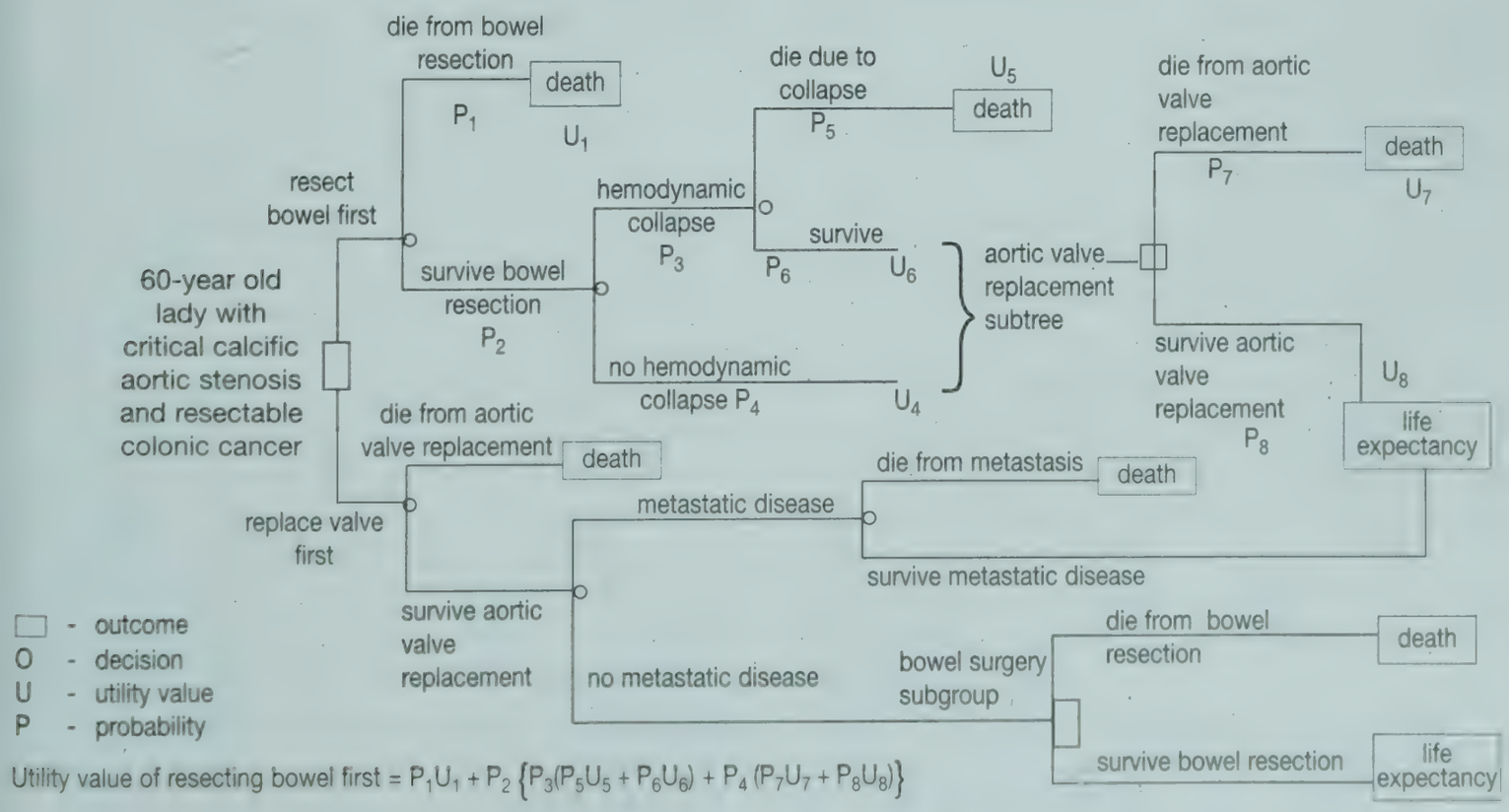


Fig 2.1 Clinical decision-making: decision design tree

KEY CONCEPTS

- Decision analysis is a systematic method of quantitative clinical reasoning.
- Data on a clinical situation *collected* and then *interpreted* by integrating the baseline *Bayesian* probability of disease with the sensitivity and specificity of the diagnostic tests used. Several management strategies can be identified; each strategy is associated with different probabilities of various possible *outcomes*. The outcomes are then *weighted* by assigning *utilities* or *values* keeping in mind the patient's preferences.
- A decision tree is used to display the temporal and logical structure of a clinical scenario. By *folding back* the tree, the optimal strategy can be defined as the branch which yields the most favourable value.

3

Genetics and Molecular Biology

BASIC GENETICS

With the exception of a few viruses, the genetic material of all organisms is deoxyribonucleic acid (DNA). DNA is a double-stranded helical polymer of nucleotides. A *nucleotide* is an adduct containing a base, a sugar and a phosphate bond. The sugar in DNA is *deoxyribose* and the base is one of the four — *adenine, guanine* (purines), *cytosine* or *thymidine* (pyrimidines). Adenine pairs with thymidine and guanine pairs with cytosine in the DNA double helix. The information content of genes resides in the unique sequence of bases along the DNA chain. Ribonucleic acid (RNA) is similar to DNA but the sugar is *ribose*, and among the bases *uracil* is found instead of thymidine.

The flow of information from the gene to its product is thus: DNA → RNA → protein. This is also referred to as the *central dogma of molecular biology*. The first step in gene expression (called *transcription*) is the enzymatic synthesis (using the enzyme RNA polymerase) of an RNA molecule that is a copy of one strand of the DNA segment. Transcription begins when the RNA polymerase binds to a sequence of bases of the DNA called the *promoter* sequence. Polymerisation continues until a *termination* sequence is reached. The product of transcription is *messenger* RNA and this is processed before it leaves the nucleus of the cell. The non-coding sequences (*introns*) are removed, the coding sequences (*exons*) are spliced together and the two termini modified by the addition of a cap at the 5′ end and a polyadenyl (A) tail at the 3′ end of the mRNA.

The messenger RNA enters the cytoplasm to be associated with ribosomes. Polypeptide chains are then synthesised by the *translation* of the messenger RNA (mRNA) molecule. Translation involves the successive reading of the base sequence of the mRNA molecule, in groups of three bases called *codons*. There are 64 codons—61 corresponding to the twenty aminoacids, the remaining three (UAA, UAG, UGA) being the *stop* codons. The code is said to be 'redundant' in that several aminoacids correspond to more than one codon. The codons in mRNA are recognised by clover leaf shaped molecules called *transfer RNA*s (tRNA) that have a three-base sequence complementary to a codon (called an *anticodon*). The tRNA molecules possess a terminally-bound amino acid and are successively hydrogen-bonded in a specific sequence to the mRNA by the codon-anticodon interaction. This stops at the stop codon and the amino acids are bound together to form a *polypeptide chain*, with the number and sequence of amino acids dependent on the base sequence of the original DNA segment (the *genetic code*). The total sequence of bases that specifies the amino acids' sequence of a single polypeptide is called a *gene* (one gene — one polypeptide chain) (Fig 3.1).

Genes determine inherited traits. Normally genes are present in pairs, one member of each pair being transmitted by each parent. A gene may exist in two or more different forms — each

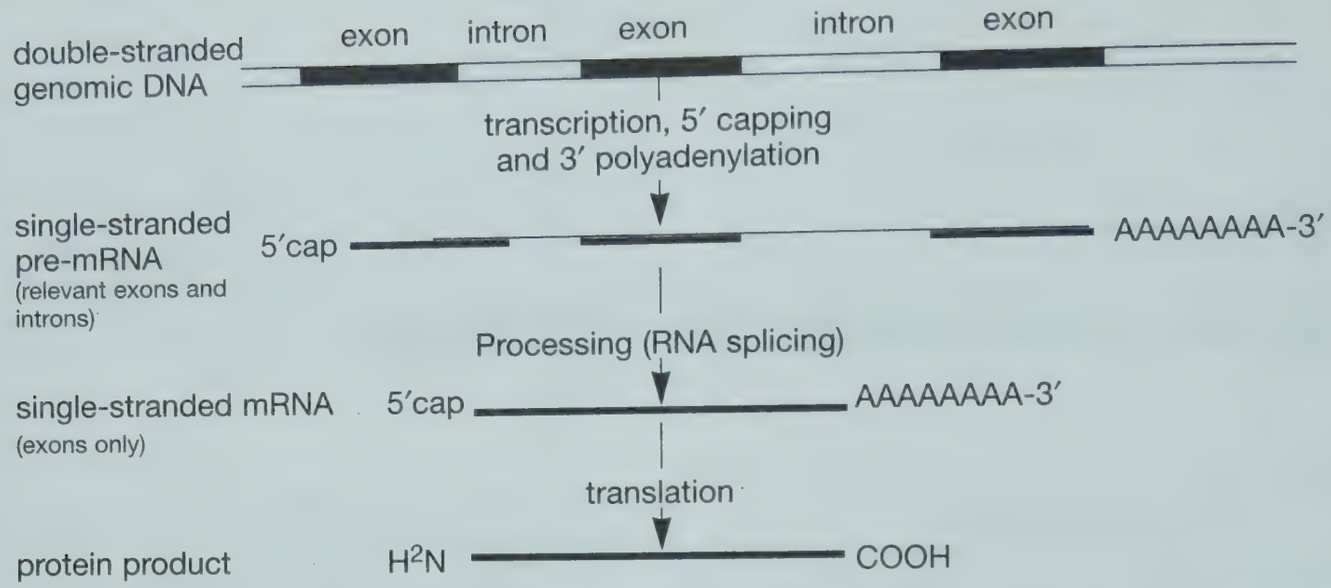


Fig 3.1 Genes contained within the DNA are transcribed into premessenger RNA and this is processed to mature messenger RNA, which is then translated into protein products which determine the functions expressed within each cell.

form being called an *allele*. The complement of alleles present in an individual constitute his/her *genotype*. The set of observable characteristics of the individual is one's *phenotype*. If the two alleles of a pair of genes are the same (for example, AA or aa), the individual is said to be *homozygous* with respect to that gene; if the alleles are different (Aa), the individual is *heterozygous*.

In eukaryotes, the DNA is condensed into structures called *chromosomes*, which are visible by light microscopy on special staining. The DNA-protein complex of a chromosome is called *chromatin* and consists of five distinct proteins (*histones* H1, H2A, H2B, H3, H4). There is a core of histones (octameric) around which the DNA is wrapped to form *nucleosomes* which are linked together to form the chromosome. In somatic cells, chromosomes occur in pairs[1] (*diploid*). Somatic cells maintain their chromosome number during mitosis. On the other hand, gametes have only one set of chromosomes (*haploid*) consisting of one member of each homologous pair. In the formation of germ cells, the diploid number of chromosomes is reduced to a haploid number by the process of *meiosis*. Before the first meiotic division, every chromosome (of a diploid set) replicates and consists of two chromatids joined by a centromere. In the first meiotic division, the sets separate so that each set still has two chromatids. In the second meiotic division, the chromatids separate and four haploid cells result. A distinctive feature of meiosis is the *side-by-side pairing* of homologous chromosomes (zygotene stage) which become connected by *chiasma* (diplotene stage). In the anaphase, the pairs separate (*disjunction*) but they may have exchanged segments during the stage of connection (*cross over*). Meiosis is the physical basis of segregation and independent assortment of genes. Non-allelic genes located on the same chromosome tend to segregate together in meiosis (that is, they are linked), a phenomenon described as *linkage*. The exchange of genetic material during cross over leads to a *recombination* of alleles. Linked genes go with each other during this recombination. In human beings, there are 46 chromosomes in each somatic cell — 44 of these are autosomes, representing the 22 homologous pairs from either parent and the other two are the sex chromosomes (XX for women, XY for men).

[1] The two members of each pair are said to be homologous.

Mutation

A mutation is a stable heritable change in DNA. It may be gross (change in part of a chromosome — deletion or insertion) or minute (change in a single base — point mutation).

GENETIC DISORDERS

Genetic disorders can be classified into four categories: 1) *chromosomal* disorders where the number or arrangement of chromosomes is different from normal and results in excess or deficient genetic material; 2) *Mendelian* disorders or monogenic disorders determined by a single mutant gene; 3) *multifactorial* disorders caused by an interplay of genetic and environmental factors, and 4) disorders with cytoplasmic *inheritance*.

Chromosomal Disorders

Chromosomal disorders are of two kinds — disorders of chromosome number and disorders of chromosome structure.

Disorders of chromosomal number

In these disorders, either a chromosome is missing (*monosomy*) or extra (*trisomy*). This may involve the sex chromosomes or the autosomes. Common autosomal and sex chromosomal monosomies and trisomies are shown in Table 3.1 alongwith their clinical features. These abnormalities are due to *non-disjunction* during meiosis (failure of two homologous chromosomes or of two sister chromatids to go to the opposite poles of the cell).

Disorders of chromosomal structure

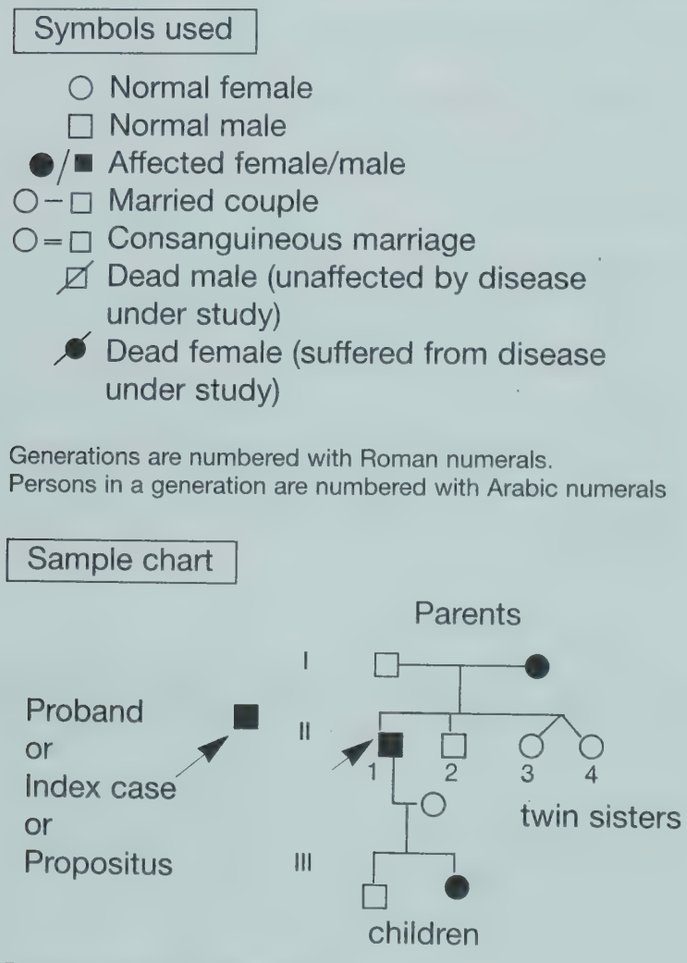
These disorders are due to a rearrangement or *translocation* of genetic material (mostly of paternal origin), which may be balanced or unbalanced. Balanced translocations are usually transmitted from generation to generation without being clinically manifest. However, certain parental translocations may predispose to progeny with unbalanced genomes. For example, maternal translocation involving chromosome 21 predisposes to fetal trisomy 21 syndrome.

Table 3.1 Some common disorders of chromosomal number

Disorder	*Eponym*	*Karyotype*	*Phenotype*
Monosomies			
Autosomal			
Chr 5	Cri-du-chat syndrome	46 XY $5p^-$	abnormal cry, microcephaly, dysmorphic features, mental retardation
Chr 13		46 XY $13q^-$	retinoblastomas, dysmorphic features, mental retardation
Sex chromosomal			
X	Turner syndrome	45 X 0	short stature, webbed neck, ovarian dysgenesis, skeletal defects, infertility
Trisomies			
Autosomal			
Chr 21	Down syndrome	47XY, +21 46/47, +21 47XX, +21	short stature, mental deficiency, hypotonia, simian crease, Brushfield's spots on iris, macroglossia, mongoloid facies
Chr 18	Edward syndrome	47XY, +18 47XX, +18	abnormal ear and facies, flared fingers, growth deficiency, early death, mental deficiency
Chr 13	Patau syndrome	47XY, +13 47XX, +13	cleft lip-palate, polydactyly, scalp defects, mental deficiency
Sex chromosomal			
X X Y	Klinefelter syndrome	47XXY 47XXX 47XYY	small testes, infertility, gynecomastia, mild mental deficiency, normal/increased height, tall, acne, reduced fertility, behavioural disorder, may be normal

Rarer chromosomal disorders include disorders with a propensity for increased random chromosomal breakages (Fanconi's anemia, ataxia telangiectasia) possibly due to *defective DNA repair mechanisms.* This also explains the increased frequency of malignancies in these disorders.

Certain other individuals exhibit chromosomal breakages at specific sites called 'fragile sites'. Such a fragile site in the X chromosome has been seen in association with mental retardation, large testes (macro-orchidism), prominent ears and jaws (*fragile X syndrome*).



Note: In taking a family history one should remember to talk to as many members of the family as possible, ask for specific symptoms and ask for details regarding 'normal' members also. One must talk to each individual confidentially and assuage feelings of guilt and fear of social stigma. Thus, in the Indian social milieu, a parent of an affected child would rarely admit to a similar illness in a sibling in the presence of others, though he/she may readily do so in private.

Fig 3.2 Pedigree chart (family tree)

Mendelian Disorders

These disorders are classified into five categories: 1) autosomal dominant, 2) autosomal recessive, 3) X-linked dominant, 4) X-linked recessive, and 5) Y-linked disorders.

A dominant[1] mutation implies that the disorder is manifest in a heterozygous state (with a single dose of the mutant gene). A *recessive* mutation requires a double dose (homozygous state) to manifest clinically. Table 3.2 demonstrates some common monogenic disorders. The observation of the inheritance pattern and distribution of traits in relatives is called its *pedigree* pattern. Fig 3.2 shows the common notations used in drawing a family tree.

Autosomal dominant (AD) traits

Autosomal genes are located on chromosomes other than the sex chromosomes. The genotype of such a trait may be AA (both dominant alleles —homozygous state) or Aa (one dominant allele —heterozygous state). Fig 3.3 shows the pedigree pattern of a typical autosomal dominant trait. Each affected individual has to have at least one affected parent and will transmit the disorder *vertically* to 50 per cent of his/her offspring. Both males and females are equally likely to be affected.[2] These disorders often have a delayed age of onset (Huntington's chorea, polycystic kidney). They are also characterised by a marked variability in the severity of expression referred to as variable penetrance.

[1] This refers to genetic traits and not to the genes themselves.

[2] Certain autosomal traits are 'gender influenced'. Thus, baldness is an autosomal dominant trait manifested mainly in men.

Table 3.2 Some Mendelian disorders

Autosomal dominant
- Marfan syndrome
- Polycystic kidney disease
- Familial hypercholesterolemia
- Huntington's chorea
- Hereditary spherocytosis
- Osler-Weber-Rendu disease
- Myotonic dystrophy

Autosomal recessive
- Sickle-cell anemia
- β-thalassemia
- Wilson's disease
- Hemochromatosis
- α_1 antitrypsin deficiency
- Phenylketonuria
- Cystic fibrosis
- Glycogen storage disease

X-linked dominant
- Vitamin D-resistant rickets
- Pseudo-hypoparathyroidism

X-linked recessive
- Hemophilia
- Glucose-6 dehydrogenase deficiency
- Duchenne muscular dystrophy
- Fabry's disease
- Colour blindness

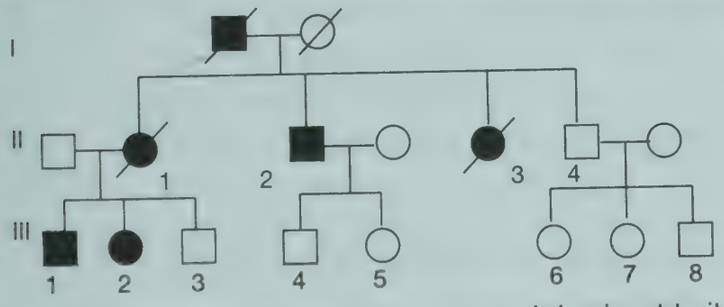


Fig 3.3 Pedigree pattern of an autosomal dominant trait, for example, Huntington's disease

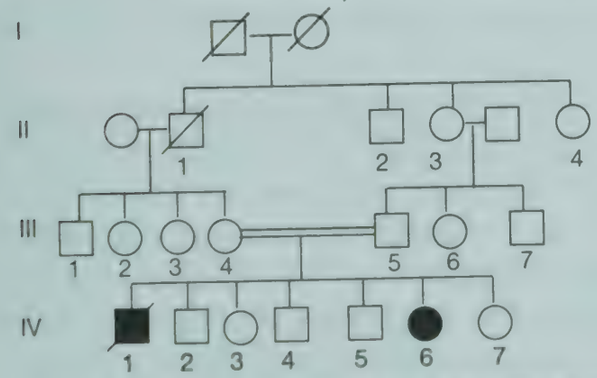


Fig 3.4 Pedigree pattern of an autosomal recessive trait, for example, cystic fibrosis

Autosomal recessive (AR) traits

The typical genotype of such disorders is aa (two recessive alleles — homozygous state). Fig 3.4 depicts the inheritance pattern of an autosomal recessive trait. The parents are often clinically normal (heterozygotes) and only siblings are affected (*horizontal* transmission). An affected individual may transmit the disorder to all, one half or none of his offspring depending on whether he marries another affected individual, a heterozygous carrier or a normal person, respectively. If two heterozygotes (carriers) marry, then a quarter of the offspring may be affected. Both males and females are equally affected. Unlike autosomal dominant disorders, these usually manifest early in life and have a uniform degree of expression.

X-linked dominant inheritance

Fig 3.5 shows the pedigree of an X-linked dominant trait. The genotype of the afflicted subject is 46 X*Y or 46 X*X where X* is the dominant mutant gene. Females are affected twice as often as males. An affected male will transmit the disorder to all his daughters but to none of his sons (who inherit his Y chromosome). A heterozygous female will transmit the disorder to half her offspring (of either sex). The disorder tends to be generally less severe in the heterozygous female than in an affected male.

X-linked recessive inheritance

Fig 3.6 depicts the pedigree of an X-linked recessive trait. The genotype of the subject is

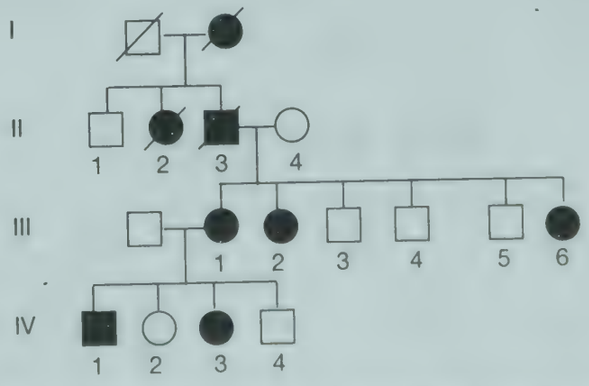


Fig 3.5 Pedigree pattern of a X-linked dominant trait, for example, vitamin D-resistant rickets

46X*Y or 46X*X*, where X* is the recessive mutant gene. Usually only males are affected; a female manifests the disease only when she is homozygous for the recessive allele. Again, an affected male does not transmit the disorder to any of his sons but the abnormal gene is passed on to all his daughters (who may be carriers if the mother is normal or may manifest the disease if the mother is a carrier or is affected by the disease). A carrier female (heterozygote) transmits the disease to half her sons or to half her daughters. Thus, if a male is affected, the sons of his carrier sister (his nephews) may be affected. This 'uncle and nephew' pattern of inheritance is called *oblique transmission.*

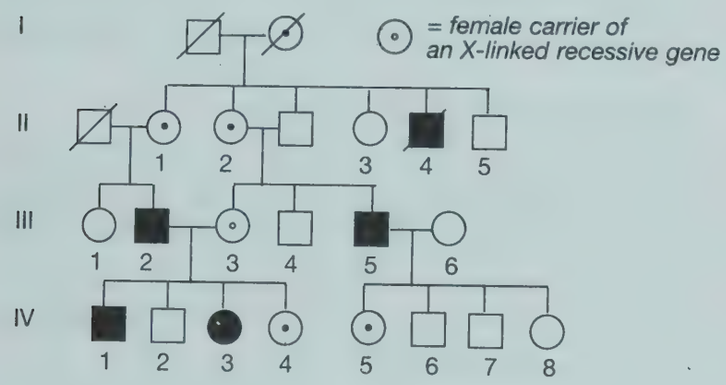


Fig 3.6 Pedigree pattern of an X-linked recessive trait, for example, hemophilia

Y-linked inheritance

A gene on the Y chromosome manifests, understandably, only in males (Fig 3.7). The genes that determine 'maleness' are Y-linked genes.

There is a group of disorders with simple Mendelian inheritance but which requires exposure to an environmental factor (usually a drug) to manifest—these are known as *pharmacogenetic disorders.* Thus, slow acetylation of isoniazid (inherited as an AR trait) can cause polyneuritis on exposure to the drug isoniazid; malignant hyperthermia (inherited as an AD trait) manifests as hyperpyrexia and muscle rigidity on exposure to certain anesthetic agents; glucose–6 phosphate dehydrogenase (G-6 PD) deficiency can lead to intravascular hemolysis on exposure of the affected individual to antimalarial drugs.

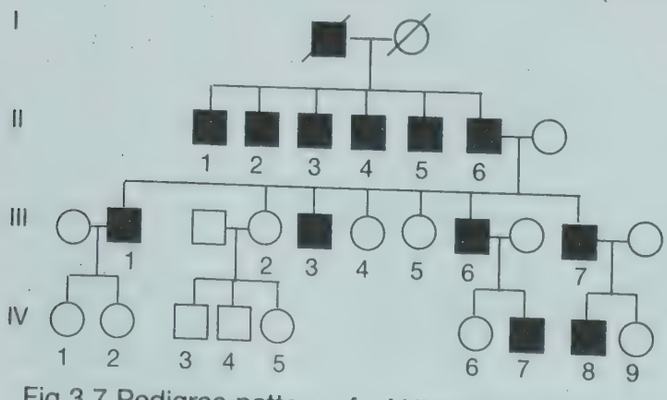


Fig 3.7 Pedigree pattern of a Y-linked recessive trait, for example, icthyosis hystrix ('porcupine-like skin')

Multifactorial Genetic Disorders

There are several traits that show continuous variation in the population in the form of a normal distribution curve. *Polygenic inheritance* is suggested for these traits and this mode of inheritance is suspected when inheritance as a simple Mendelian trait is not likely on pedigree analysis. In multifactorial genetic disorders there is a polygenic component as well as an environmental component. An individual with a requisite assortment of risk genes passes beyond a *risk threshold* and a further expression of these risk genes is then determined by environmental factors. The incidence of disease in the first degree relatives of an affected subject is equal to the square root of the frequency of the disease in the general population. These multifactorial disorders are also seen to demonstrate the *Carter effect*, where children are more likely to inherit the disease from a parent of the less frequently affected sex. The common diseases said to 'run' in families belong to this category, for example, hypertension, coronary artery disease, diabetes mellitus, peptic ulcer, schizophrenia, and cleft lip and palate.

The fact that upto a third of all human genetic loci contain polymorphic alleles has been cited as evidence for the multifactorial inheritance model and may provide the basis for individual variation in genetic susceptibility. In humans, the human leukocyte antigen system (HLA) or the major histocompatibility locus (MHC) is the genetic locus more often associated with disease. It is discussed in detail elsewhere. Briefly, the

allele HLA B-27 is associated with an increased risk of seronegative spondyloarthropathies, HLA B-8 with myasthenia gravis, HLA DR 3/4 with increased risk of insulin-dependent diabetes mellitus.

Disorders with Cytoplasmic Inheritance (Mitochondrial Inheritance)

In humans (as in other eukaryotes) the mitochondria contain circular chromosomes that code for certain ribosomal RNA and for polypeptides involved in oxidative phosphorylation. This mitochondrial DNA may transmit traits in a manner that does not follow Mendelian principles. Since the bulk of cytoplasm in a zygote is of maternal origin (the sperm contains very little cytoplasm), the mitochondrial DNA of an individual is of maternal origin. Thus cytoplasmic inheritance (mediated by mitochondrial DNA) is *maternal inheritance*, that is, the trait is passed on from a mutant mother to her offspring but not from a mutant father to his children. *Leber's optic atrophy* and the *ragged red fibre myopathy* are disorders with exclusive maternal transmission and therefore were long assumed to indicate cytoplasmic inheritance. Recently, the mitochondrial gene responsible for Leber's optic atrophy has been detected, thus confirming the hypothesis.

Genetic Heterogeneity and Pleiotropism

Genetic heterogeneity means that a particular phenotype can result from any one of separate genotypes. Thus, Marfan syndrome and homocystinuria are both associated with a similar phenotype (of subluxation of ocular lenses and skeletal abnormalities). The genotypes, the mode of inheritance and the prognosis of these 'lookalikes' are, however, different.

Pleiotropism[1] means that a single gene can result in several phenotypic features. A conglomeration of the several features is often called a 'syndrome'.[2] Thus the association of melanin spots of the buccal mucosa, lips and digits with jejunal polyps (referred to as *Peutz-Jeghers syndrome*) may be due to the pleiotropic effects of an unidentified gene.

TECHNIQUES IN MOLECULAR BIOLOGY

Recombinant DNA Technology

DNA cloning—a general strategy

The method of faithfully copying, in vivo, individual DNA molecules to produce numerous identical molecules (clones) is called *cloning*.

Linear DNA molecules are mixed with the DNA of a vector and the two are joined together using the enzyme 'DNA ligase'. The resultant DNA is called *recombinant DNA*, that is, DNA from different sources joined together. The vector is either a plasmid (circular DNA molecules that can replicate independently of the bacterial chromosome) or a bacteriophage (bacterial viruses). The recombinant DNA is entered into a suitable host cell which provides the enzymatic machinery necessary for generating copies of the recombinant DNA molecules. The most commonly used host cell is a laboratory strain of the gut bacterium, *Escherichia coli.* Host cells are then grown and multiplied on agar plates (Fig 3.8).

Restriction enzymes For the generation of linear DNA and linearised vector DNA, enzymes that cut DNA at specific DNA sites are used. These enzymes are called *restriction enzymes* and the sites *restriction sites.* For instance, the enzyme *Eco RI* recognises the palindromic[3] sequence

5′ G A A T T C – 3′
3′ C T T A A G – 5′

When the total genomic DNA is used to produce a collection of recombinant molecules, it is called a genomic *library* of recombinant

[1] Pleiotropism: multiple effects

[2] Syndrome : 'running together'

[3] Reading the same backward and forward e.g. Bob

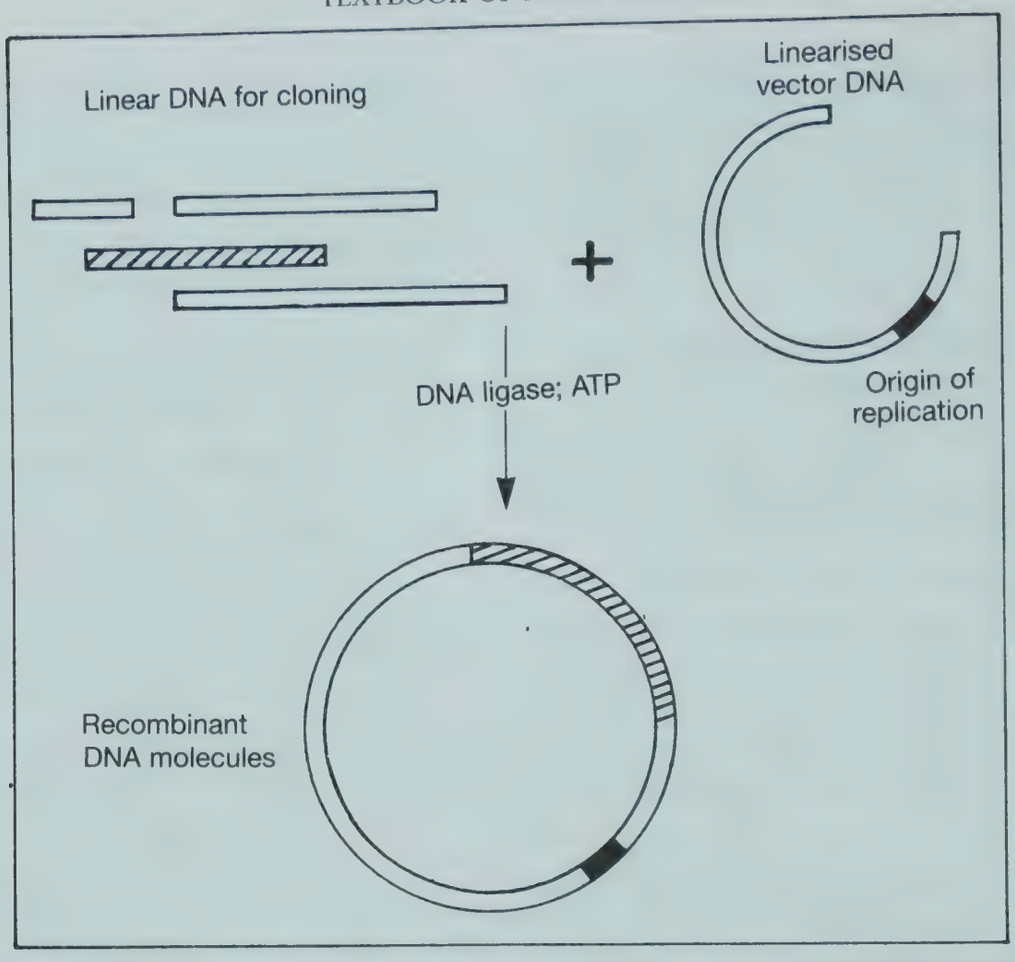


Fig 3.8 General strategy for DNA cloning (with plasmid vector). Linear fragments of DNA for cloning (usually produced by digestion with restriction enzymes) are joined to vector DNA molecules in vitro, with the enzyme DNA ligase. As the vector is a plasmid the resulting recombinant DNA molecules are circular. Plasmids contain a sequence which initiates replication (origin of replication) which allows them to be copied by the host cell.

DNA. Similarly, messenger RNA can be used to generate *complementary DNA* (*cDNA*) by subjecting it to the action of the enzyme *reverse transcriptase* and cloning the synthesised DNA. These are called cDNA libraries. cDNA differs from genomic DNA in that it has no introns (Fig 3.9 a, b).

Synthetic single-stranded DNA molecules referred to as *oligonucleotides,* can be used as probes for selecting a clone producing a DNA sequence complementary to that of the probing molecule.

Clinical applications Recombinant DNA technology has enabled scientists to prepare several biosynthetic products using the corresponding gene clones, for example, insulin, growth hormone, factor VIII and tissue plasminogen activator (TPA). It has permitted the changes in nucleotide sequences in various disorders to be determined, and its role in prenatal diagnosis and gene therapy is discussed in later sections.

Electrophoresis of Proteins and Nucleic Acids

SDS-PAGE system

Sodium dodecyl sulphate (SDS)-polyacrylamid gel electrophoresis (PAGE) separates poly peptides according to their size, with the rate o migration varying inversely with the molecula weight of the polypeptide. SDS is a bufferin detergent which denatures proteins in such way that individual subunits of the protein dissociate themselves. After applying th protein sample (test sample) near the cathod end of a slab of gel, an electric field i applied and the protein SDS complex migrate towards the anode. The sieving properties o polyacrylamide separate out the proteins, and b running a sample of standard protei (with known molecular weight) and comparin

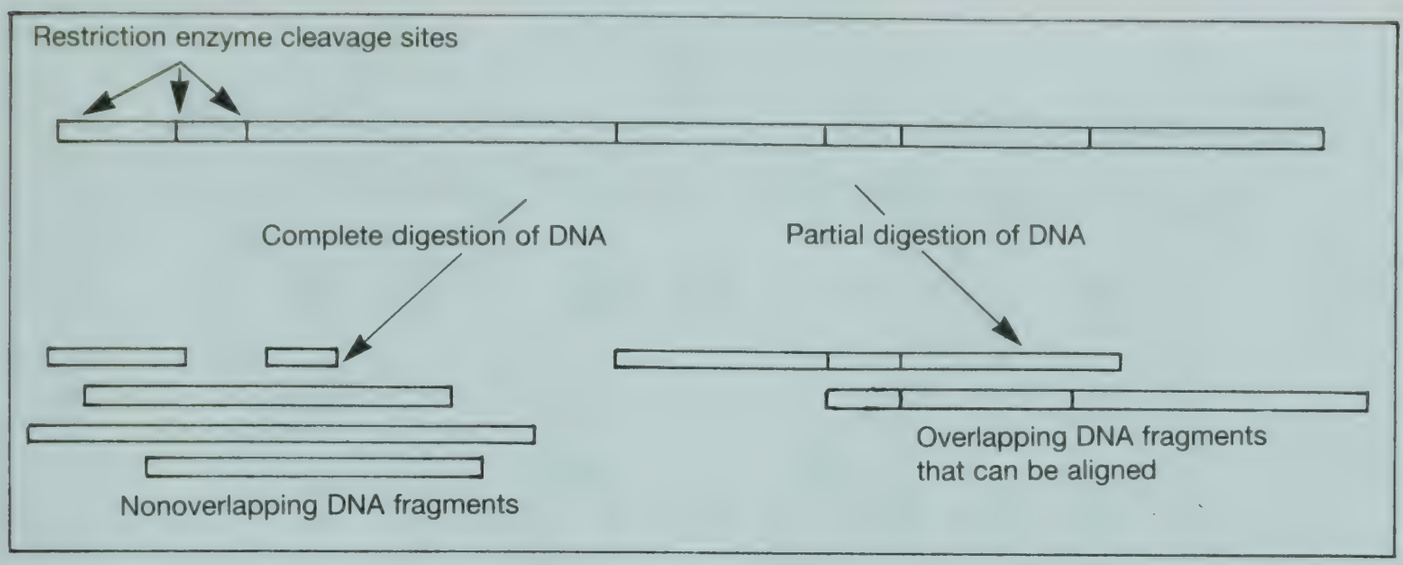


Fig 3.9 a Complete digestion of DNA with a restriction enzyme produces non-overlapping DNA fragments and all information as to the order of the fragments is lost, whereas partial digestion yields overlapping fragments of DNA to be cloned in the library; these can be ordered later into a physical map.

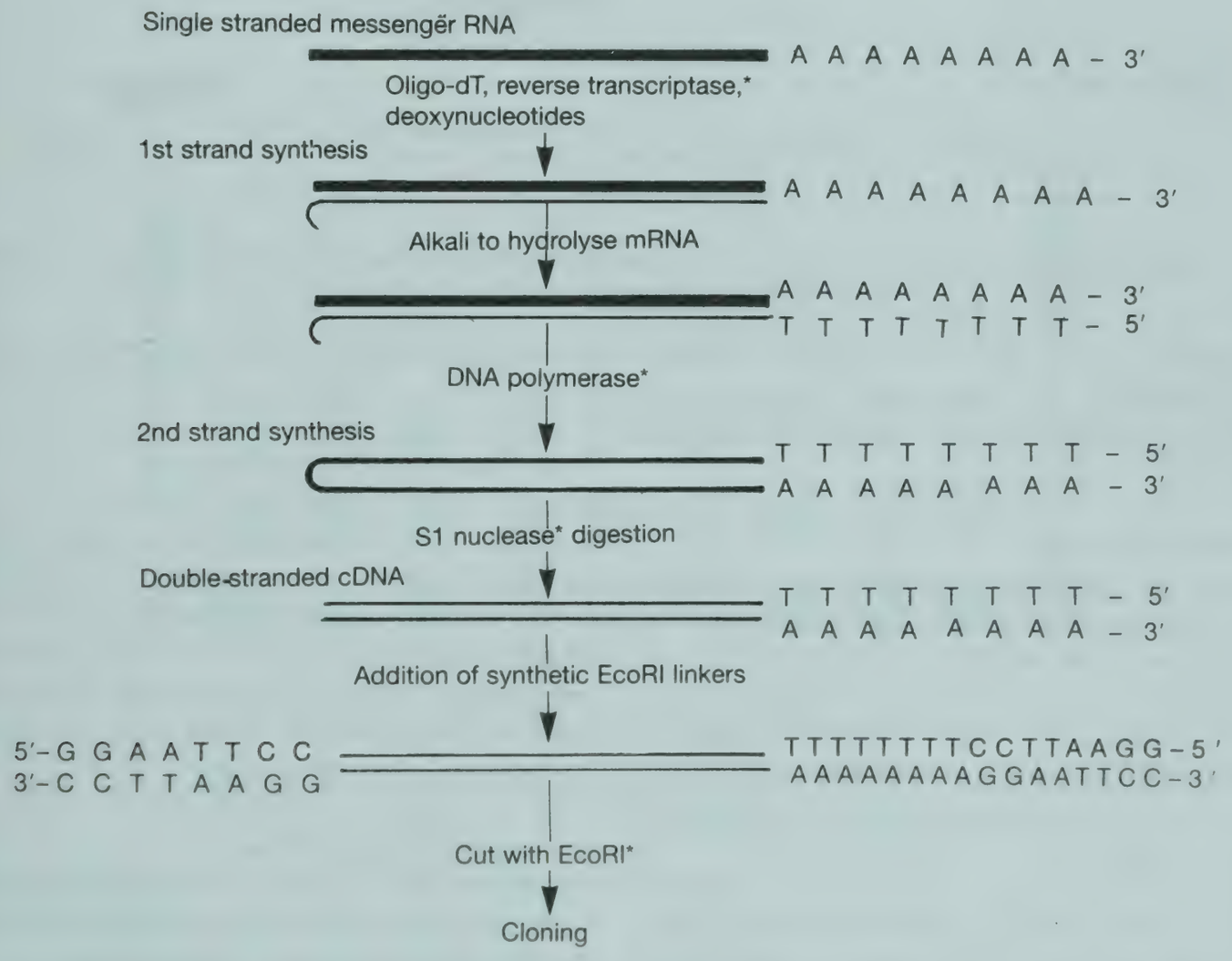


Fig 3.9b Conversion of single-stranded mature messenger RNA into double-stranded complementary DNA in vitro with purified enzymes to catalyse the reactions

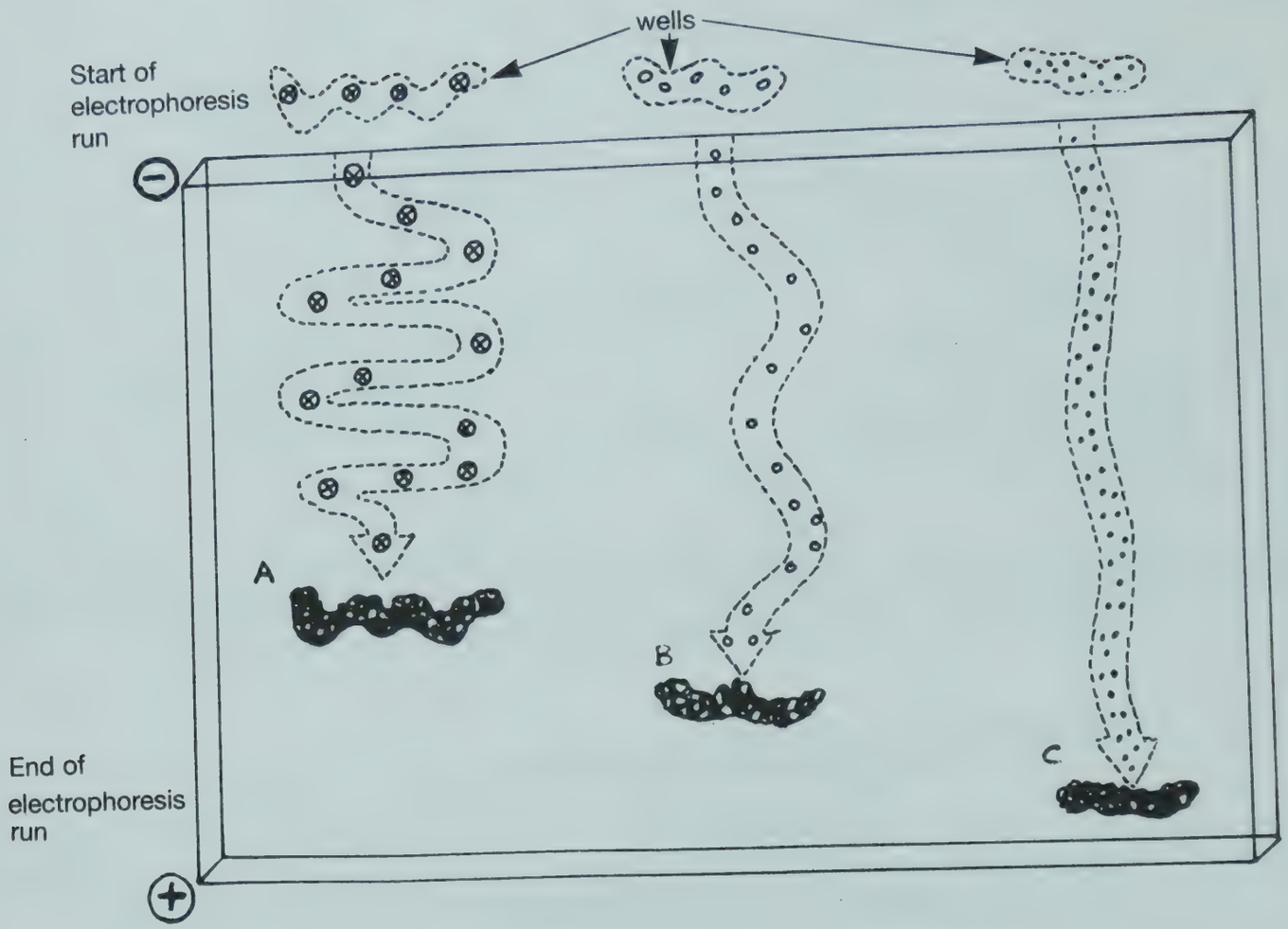


Fig 3.10 In SDS-PAGE the gel matrix acts as a molecular sieve so that peptides of high molecular weight migrate most slowly (molecular weight of protein A > B > C).

its mobility with that of fragments in the test sample, the molecular weight of various fragment peptides can be determined (Fig 3.10).

Isoelectric focussing

Proteins are *amphoteric* molecules with their charge (determined by the ionisable amino acid side chains) varying with the pH. Thus, at low pH proteins tend to be positively charged and at higher pH they become negatively charged. The pH value at which the net charge on a protein is zero is the isoelectric point (PI), which generally lies between pH 4 and pH 7. In isoelectric focussing, electrophoresis is carried out in a continuous pH gradient increasing from the anode to the cathode (Fig 3.11). A protein will migrate to a position in the pH gradient where its net charge is zero. This focussing concentrates the proteins into very narrow bands.

Two-dimensional electrophoresis

When either of the above methods is used in isolation, it is still possible for a single electrophoretic band to be composed of different proteins which comigrate. The best resolution is therefore, achieved by separating the proteins by one method and then applying the second method at right angles to the first, that is, two-dimensional electrophoresis.

Agarose gel electrophoresis

For separating out nucleic acids, agarose gel is the best sieve (the pore size, being larger, is ideal for large molecules). Agarose gel electrophoresis is of central importance in DNA sequencing.

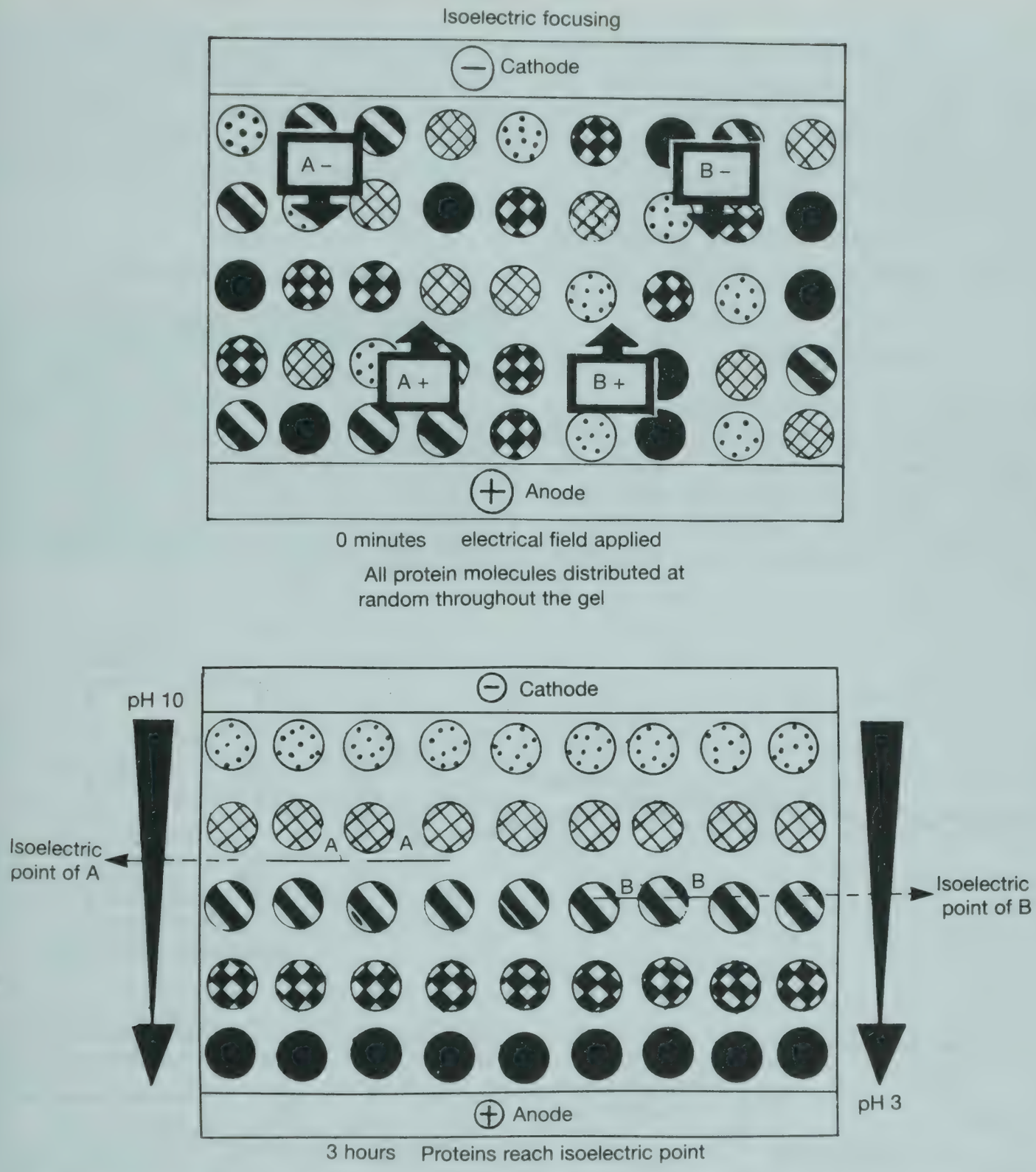


Fig 3.11 In isoelectric focussing protein samples (A and B) migrate in a pH gradient until each reaches its own isoelectric point. (The isoelectric point is a pH value and not a place on the gel.)

Clinical applications Serum electrophoresis is normally carried out on cellulose acetate (*zone electrophoresis*) which yields only low resolution separation, but is sufficient for demonstrating gross abnormalities such as a paraprotein spike (M spike) in multiple myeloma. Agarose gel electrophoresis makes it easier to recognise more subtle changes. SDS-PAGE provides still higher resolution but is costly. SDS-PAGE is useful in evaluating glomerular proteinuria, studying isoenzymes of alkaline phosphatase and for monitoring the purity of –

proteins (a single band being a criterion of purity). Isoelectric focussing is used to identify oligoclonal IgG bands in the cerebrospinal fluid of a patient with multiple sclerosis, identifying various phenotypes of alpha-1 antitrypsin, separating Hb A_1c in diabetics, etc. Two-dimensional electrophoresis, being more cumbersome, is mainly a research tool.

Blotting Techniques

Specific proteins in complex biologic mixtures and abnormal genes in the genomic DNA can be identified by techniques referred to as *blotting* techniques. There are three types of blotting techniques which are based on the same principle but carry different names depending on the substance identified (Table 3.3). Thus *Southern blotting* (named after its originator E.M. Southern) identifies DNA fragments, *Northern blotting* identifies messenger RNA and *Western blotting* identifies particular proteins.

Table 3.3 Types of blotting techniques

Technique	*Material identified*	*Method*
Southern blot	DNA	Nucleic acid hybridisation
Northern blot	RNA	Nucleic acid hybridisation
Western/ Immunoblot	Protein	Immunologic identification

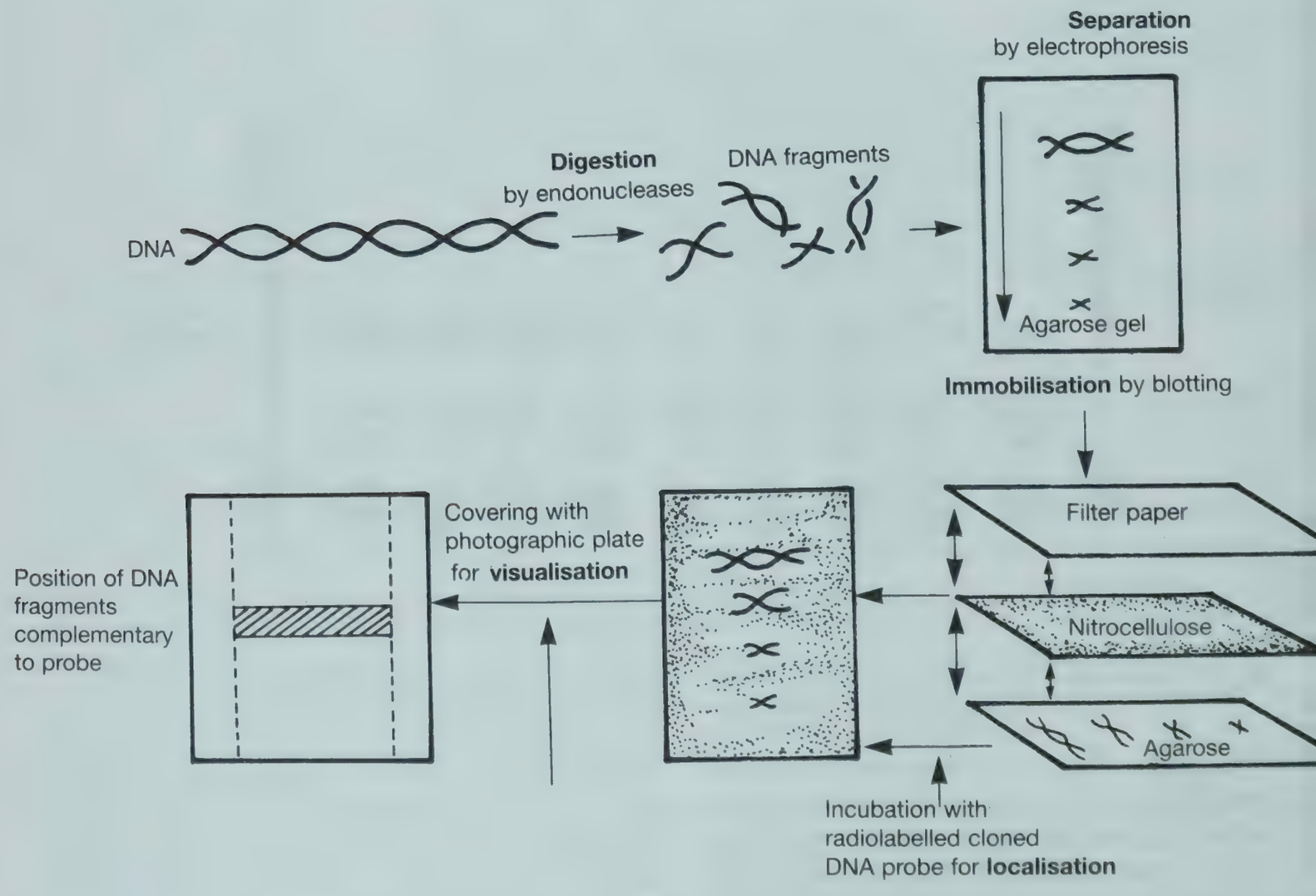


Fig 3.12 Southern blotting for identification of DNA fragments

General principles Four basic steps are involved in the blotting process (Fig 3.12). The first step is the separation of molecules in the sample by electrophoresis. This is followed by the transfer to and immobilisation of the molecules, on an easily handled support medium (nitrocelluose paper) or membrane (polyvinylidine difluoride)— a process which facilitates further analysis. The third step is to localise the immobilised protein or nucleic acid fragment by the use of probes that specifically bind to the molecule of interest. Thus, DNA and RNA are identified using nucleic acid (DNA) probes which hybridise by hydrogen bonding to complementary sequences, and proteins are identified by using specific antibodies as analytical probes. The last step is to visualise the molecule by *autoradiography*.[1]

Applications *Southern* blotting is used for identifying genes associated with genetic diseases, for example, Huntington's chorea gene, cystic fibrosis gene. It has also been used to investigate the biology of malignant tumours, for example, detection of hepatitis B virus genome in the genomic DNA of hepatocellular carcinoma cell lines. *Northern* blotting helps to study the products of gene transcription, for example, multiple drug resistance associated with certain malignant tumours is due to increase in RNA transcribed by the MDR-I gene. *Western* blotting is used widely in screening for the acquired immunodeficiency syndrome. Thus, antibodies (against certain HIV proteins) in the patient's serum are used as probes to show the presence of known viral antigens that have been run onto an electrophoretic strip.

[1] The process in which the radioactivity of isotopes is detected by applying a photographic film onto the isotope-labelled probe

The Polymerase Chain Reaction

The *polymerase chain reaction* is a simple though ingenious method of amplifying a desired segment of DNA by a millionfold in a few hours' time, without requiring purification of DNA, recombination with a vector or the use of bacterial cultures.

Before a strand of DNA can be synthesised, a piece of complementary DNA called a *primer* must attach to a portion of the template strand and prepare (or 'prime') it for the action of DNA polymerase. The latter extends the primer by adding further nucleotides complementary to the template. A prerequisite, therefore, is knowledge of the base sequence of regions flanking the desired DNA segment to be amplified. This would enable the selection of two oligonucleotide primers, complementary to the flanking sequence on either side and on opposite strands of the target segment (Fig 3.13 a,b,c). When these primers are hybridised to DNA (in histologic sections or tissue homogenates or body fluids) and DNA polymerase is added, the amount of the desired DNA segment increases in a logarithmic fashion.

The first step is the *heat denaturation* of the native double-stranded DNA (from any clinical, laboratory, forensic or archeological specimen) which liberates single strands of DNA. The next step is *primer annealing* — the addition of complementary DNA primers that 'anneal' to the template. This step requires the temperature to be lowered. The third step is *primer extension* or target DNA synthesis. In this the heat-stable *enzyme Taq DNA polymerase* (obtained from the thermophilic bacillus *Thermophilus aquaticus*) is added along with deoxyribonucleoside triphosphates. The cycle is repeated in an automated method resulting in *cell-free molecular cloning.*

The reaction has been used for *forensic* purposes to identify the source of blood stains, hair or sperm. It has also been used for the detection of *infectious* diseases, for example,

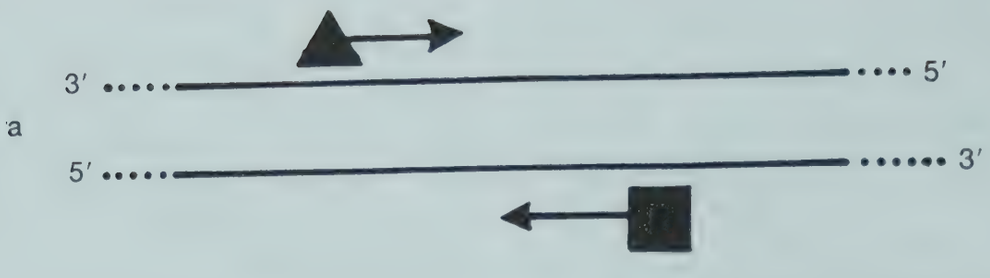


Fig 3.13a Principle of the polymerase chain reaction: the diagram shows part of a sample of double-stranded genomic DNA (parallel horizontal lines) with unique attachment sites for oligonucleotide primers (triangle and square) of the enzyme DNA polymerase which directs DNA synthesis in the direction of the arrows. The two primers define the limits of the desired site of DNA replication.

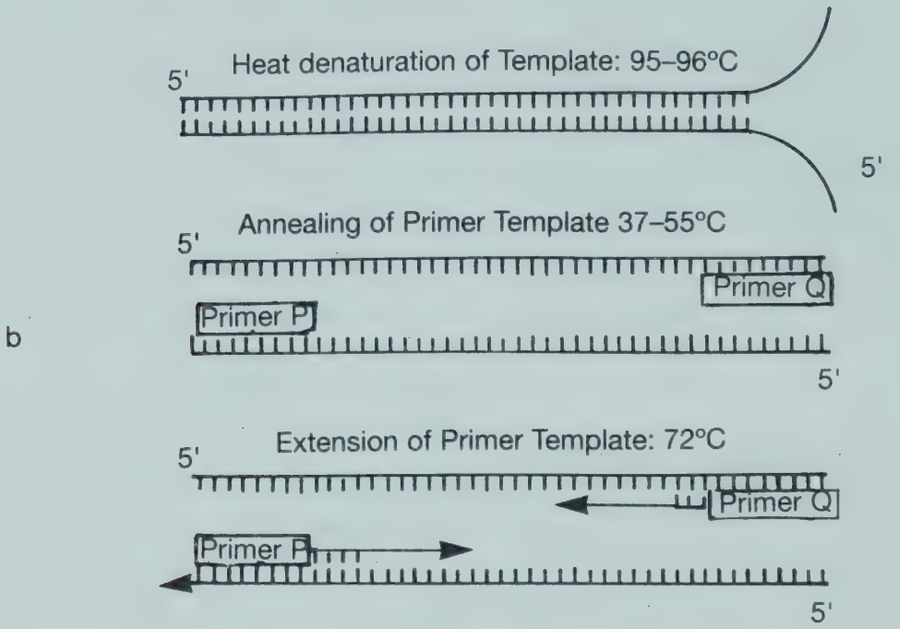


Fig 3.13b The three basic PCR reactions occur at different temperatures

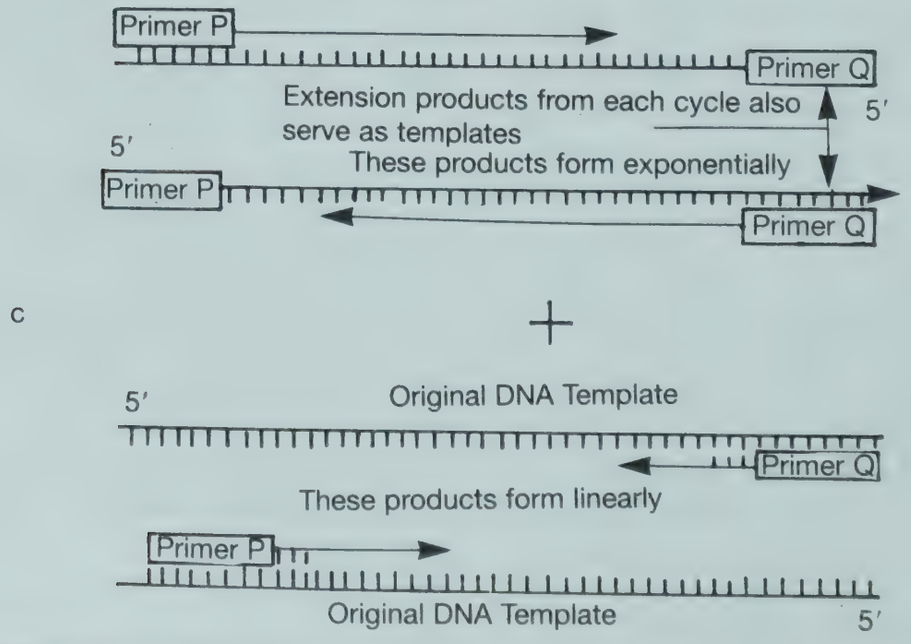


Fig 3.13c Exponential accumulation of the target sequence occurs because the extension products from previous cycles can all serve as templates in subsequent cycles.

detection of HIV genome in subjects at risk, detection of *Mycobacterium tuberculosis* in the CSF of patients with tubercular meningitis, detection of enteroviruses in the endomyocardial biopsies of patients with viral myocarditis. The polymerase chain reaction has been used for the diagnosis of *genetic disorders* where the defective gene is known, for example, sickle-cell anemia, β-thalassemia, Huntington's disease, hemophilia, cystic fibrosis, Duchenne muscular dystrophy.

It must be remembered, however, that the extraordinary sensitivity of the test (its greatest virtue) is also its greatest limitation. False positive reactions from carry-overs of previously amplified DNA or from cross-contamination by true positive samples are a major drawback, necessitating meticulous laboratory techniques.

Linkage Map of the Human Genome

When the affected gene cannot be identified, the technique of linkage can be used for genetic diagnosis. The concept of linkage involves finding some trait that is genetically linked to the pathologic trait, that is, the genes for the two traits are so closely 'linked' (by virtue of being near each other on the genome) that during the exchange of chromosomal material in meiosis they will generally stay together and be exchanged (or not exchanged) as a unit. If the pathologic gene is linked to a segment of DNA that is *polymorphic* (of several types), and in a given family we know that the pathologic gene is

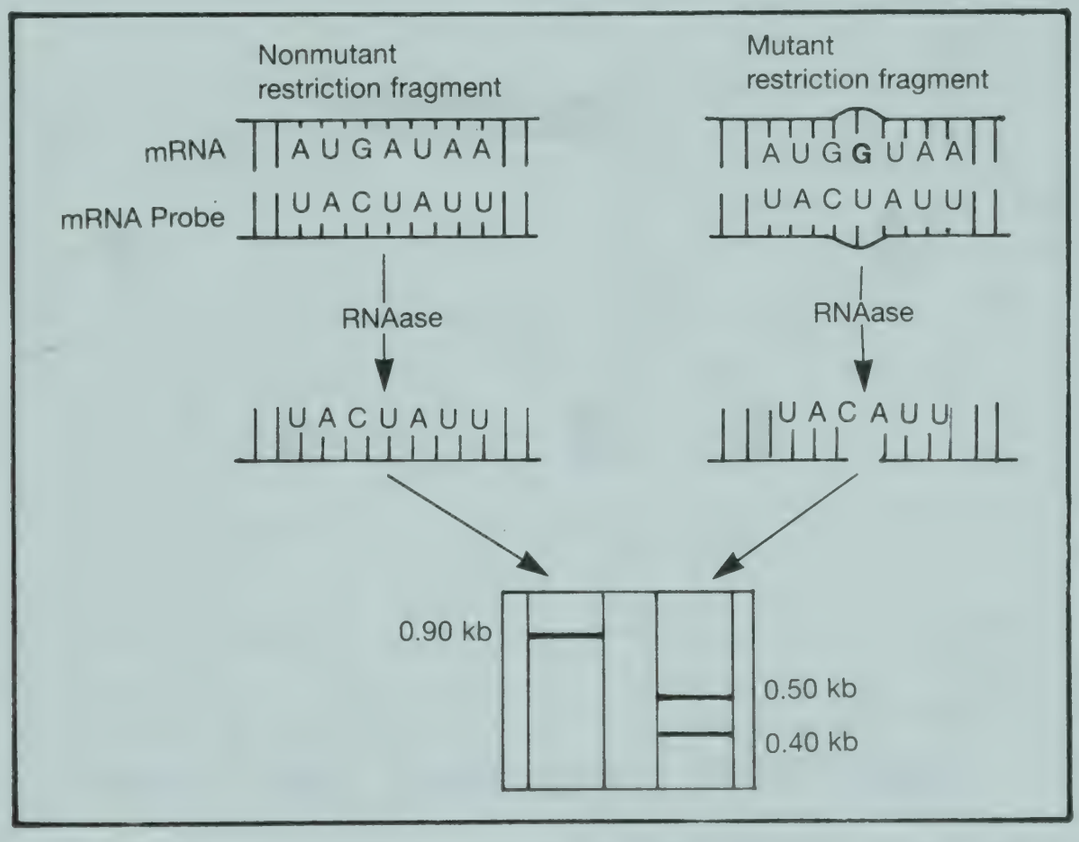


Fig 3.14 Oligonucleotide probes can detect mutations of a single base pair because such mutations produce a mismatch between the probe, keyed to the normal gene, and the mutant mRNA. The radioactively-labelled probe binds tightly to the small segment of the normal gene to which it is complementary (left), so that when treated with RNAase it is not cleaved; on denaturation it shows up on a radioautograph as a single band. However, when a mutation is present (right) the mismatch allows the RNAase to break the RNA probe at that point, producing two bands in the radioautograph. The molecular weights of the two bands will equal that of the single band from the normal DNA, and the site of the mutation can be inferred from the relative sizes of the two pieces. kb refers to kilobases, a measure of weight of DNA.

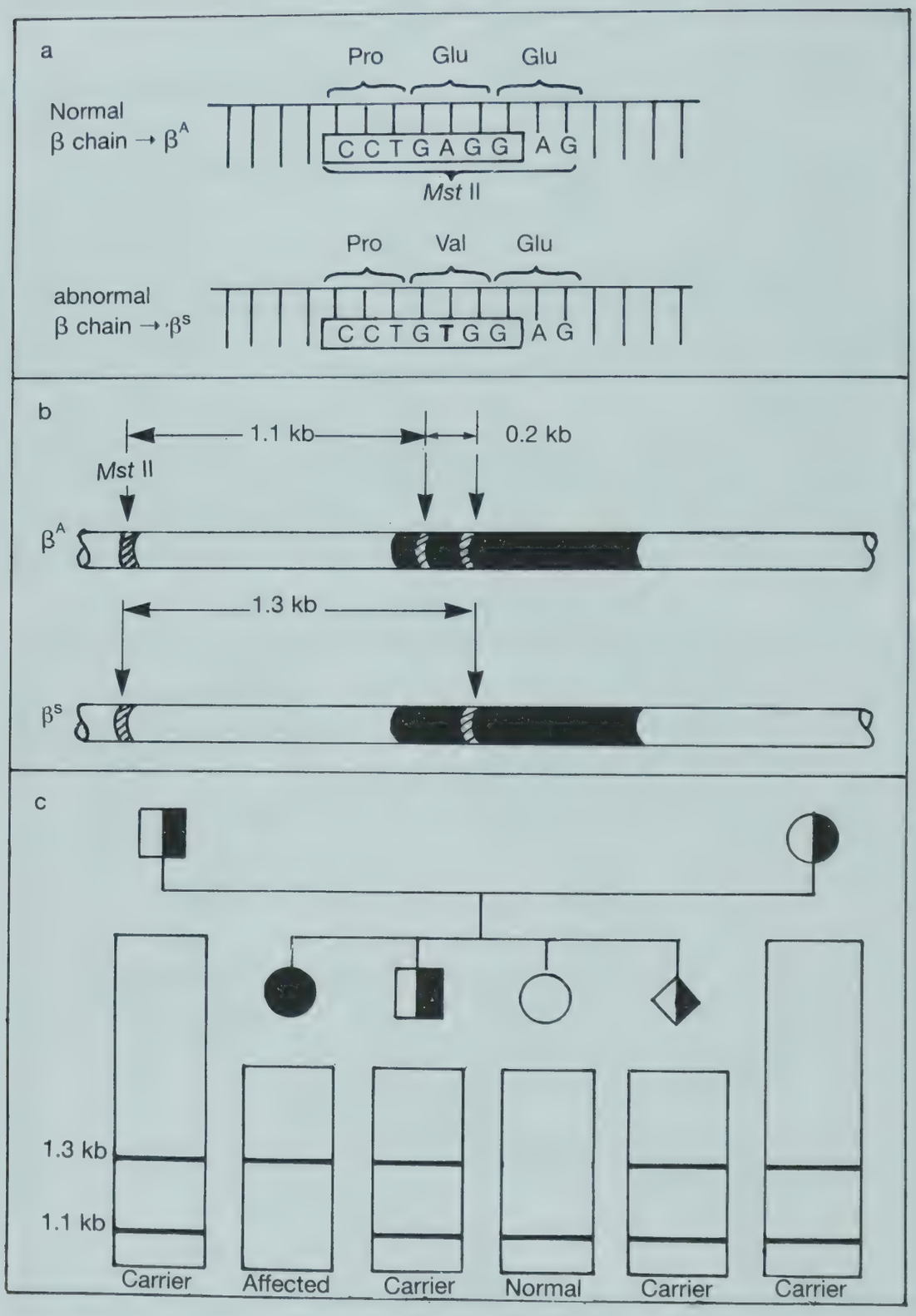


Fig 3.15 The single base error that causes sickle cell disease is one of the few point mutations which can b detected directly by a restriction fragment length polymorphism (RFLP). The base change in the hemoglobi ß chain (a) abolishes one of the MST II recognition sites on a Southern blot labelled with a ß-globin probe (b) A DNA sample treated with that enzyme MST II produces a single 1.3 kb fragment instead of the normal tw fragments of 1.1 and 0.2 kb. Normal individuals show only the 1.1 kb fragment (the 0.2 kb one is 'lost' in processing) homozygous (affected) individuals show only the heavier fragment, whereas heterozygotes (carriers) show bot the 1.1 and 1.3 kb fragments. In the family shown here (c), both parents are carriers; of their three children one is affected, one is a carrier, and one is normal. Their fetus, whose DNA was under examination (diamond is a carrier.

linked to one of these polymorphisms (types), then detection of that polymorphism in a given individual would identify the presence of the pathologic gene in him.

DNA polymorphism is a central and benign feature of the human genome. By this we mean that a small number (0.1%) of base pairs in the human DNA may vary from individual to individual, without producing functional differences. However, this change in base pairs can be associated with production of an additional site for action of the restriction endonucleases (called restriction site) or with the abolition of a preexisting site. Either way, the change in base pairs (referred to as *polymorphism*) may render itself obvious by variable lengths of restriction fragments due to a change in the number of restriction sites. This phenomenon is referred to as *restriction fragment length polymorphism* (RFLP). If such a polymorphic site is located within 10 million base pairs from the pathologic gene, the two would segregate together and the gene would be identified by the RFLP.

These RFLPs can be easily assayed in individuals. A small volume of peripheral blood provides sufficient lymphocyte DNA for analysis. Restriction fragments may be displayed by electrophoresis in agarose gels, separating the fragments according to their molecular size (which in turn would depend on their length) (Fig 3.14). Further, the RFLPs are inherited according to simple Mendelian principles and permit linkage mapping of the human genome. The use of RFLPs for the diagnosis of sickle-cell anemia is depicted in Fig 3.15.

PREVENTION AND TREATMENT OF GENETIC DISORDERS

Genetic counselling and early prenatal diagnosis are the two ways to prevent the occurrence of genetic disorders.

Genetic Counselling

The first step in genetic counselling is to establish the diagnosis in the parent or the affected child. This involves detailed clinical evaluation, pedigree analysis and specialised laboratory tests (cytogenetic analysis for the karyotype). Once the diagnosis is established, an empirical *probability* of the disease in future children can be calculated based on empiric risk rates available for various disorders. The next stage is *informative counselling* in which the various options and prognosis of the disease are discussed with the counselees. The last step is to help the counselees to choose, and to support them in their decision.

Prenatal Diagnosis

The three main diagnostic techniques available are *chorionic villus biopsy, amniocentesis* and *ultrasonography.* Chorionic villus sampling is usually carried out at 8–12 weeks gestation. DNA is extracted from the chorionic sample and a DNA probe is used to determine whether the specific gene coding for a disorder is present; for example, gene probes for cystic fibrosis, Duchenne muscular dystrophy and hemoglobinopathies are available. The main indications include fetal chromosomal analysis, fetal sexing,[1] enzyme assays and gene probe assessment. The risk of abortion is 3–5 per cent (marginally more than the 2–3 per cent incidence of spontaneous abortions).

Amniocentesis is performed at 16–18 weeks. The amniotic fluid levels of alpha fetoprotein are elevated when the fetus has anencephaly or a myelomeningocele. The fluid can be used for chromosomal analysis, enzyme analysis, or for DNA studies (Fig 3.16 a,b). Raised maternal serum alpha fetoprotein levels is itself an indication for amniocentesis so that a neural tube defect can be confirmed or ruled out.

[1] This is done for sex-linked disorders such as hemophilia. Its use for purely determining gender is unethical.

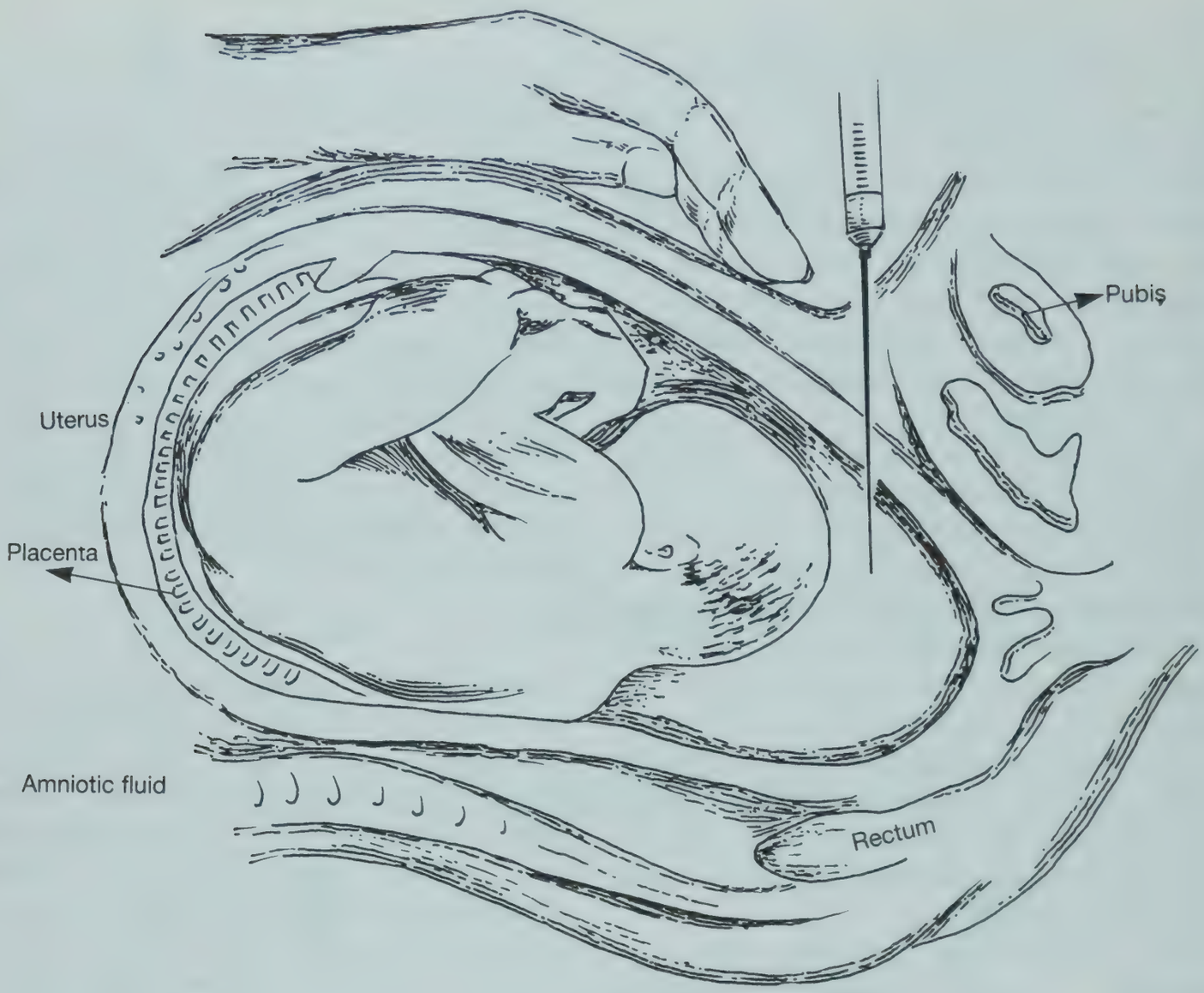


Fig 3.16a Amniocentesis—technique of suprapubic aspiration

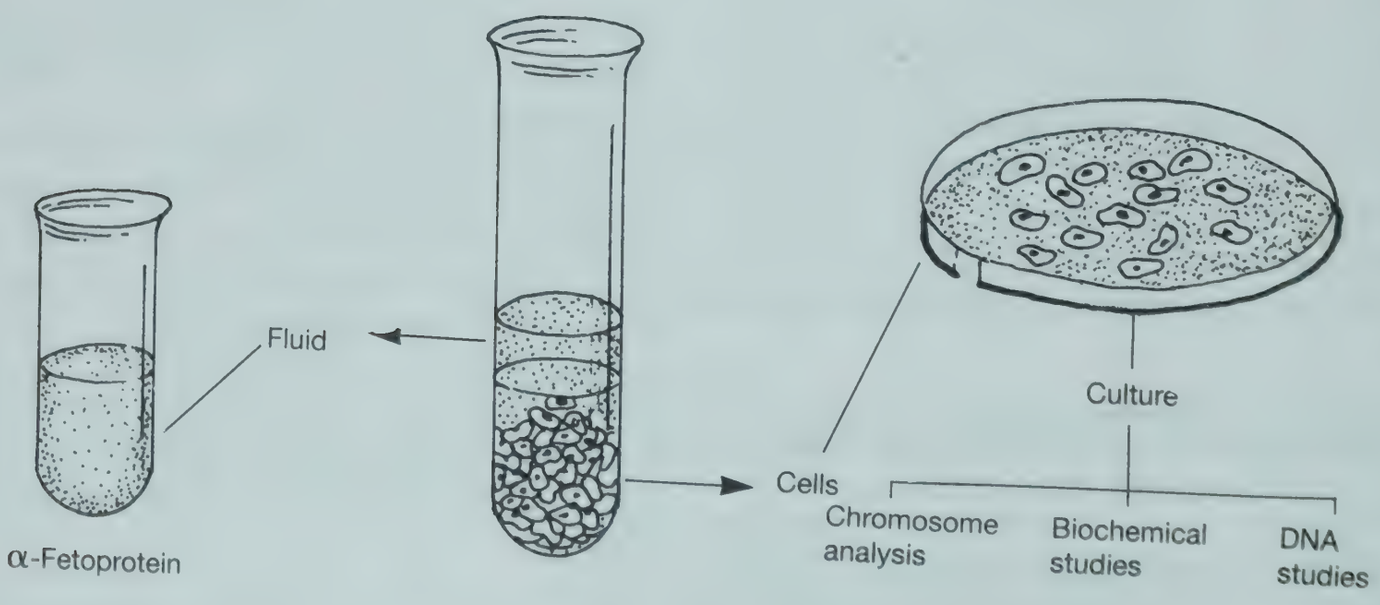


Fig 3.16b Amniocentesis—analysis of aspirate

Ultrasonography is performed routinely at 16–18 weeks gestation to look for gross anomalies of the central nervous system, kidneys, heart and the skeleton. Ultrasound-guided *cordocentesis* (taking blood from the umbilical cord) has also been done at 18–20 weeks for chromosome studies, enzyme estimations and gene probe techniques. A low hematocrit of cord blood may indicate rhesus incompatibility.

Secondary prevention

Whereas the aim of genetic counselling is primary prevention, it is now possible to conceive of *secondary prevention* by early detection of genetic diseases and prompt initiation of therapy to avoid the effect of the diseases. For example, neonatal screening and identification of phenylketonuria and galactosemia have led to early institution of a phenylalanine-free and galactose-free diet, respectively, before irreversible damage can occur. Similarly, the preclinical state can be detected in Wilson's disease and hemochromatosis in asymptomatic siblings of affected patients and measures to reduce body copper and iron, respectively, instituted before any damage can occur. In recessive disorders, the screening of siblings is usually an adequate measure. The heterozygote carriers once detected are given genetic counselling and their pregnancies are monitored.

For dominant disorders such as acute intermittent porphyria, it is essential to screen all first-degree relatives (parents, siblings and offsprings).

Gene Therapy

Gene therapy can be classified into three categories:

1. repair of defective genes in inborn genetic disorders (adenosine deaminase deficiency, sickle-cell anemia);
2. cellular replacement therapy (Parkinsonism, diabetes, muscular dystrophies);
3. addition of new genes for therapeutic purposes.

In serious genetic disorders such as adenosine deaminase (ADA) deficiency, conventional enzyme replacement is very costly. In this rare disorder, toxic byproducts of nucleotide metabolism accumulate in the immature T lymphocytes (due to ADA deficiency, a key enzyme in the metabolic pathway) and the latter cells die resulting in a severe immunodeficiency state. Trials are continuing to insert the ADA gene into lymphocytes using retrovirus-mediated gene transfer, hoping to provide an alternative to conventional therapy (Fig 3.17 a,b).

Cellular replacement therapy consists of transplanting dopamine-producing cells in Parkinsonism, myoblast grafting in Duchenne muscular dystrophy (in humans) and pancreatic beta cell transplantation into thymic tissue, where they are recognised by the immune system as 'self' (in experimental animals).

Gene therapy is also being used for engineering new therapies for cancer. The lymphocytes infiltrating malignant tumours (called *tumour infiltrating lymphocytes* or *TIL*) are cultured in media containing interleukin 2 which stimulates them markedly. Then the gene for the *tumour necrosis factor* (TNF—a highly toxic glycoprotein produced by the macrophage) is introduced into the TIL and the latter transfused into patients with tumours. This form of therapy is experimental at the moment.

Future trials are likely to be targeted against other diseases such as Gaucher's disease, hemophilia and α_1 antitrypsin deficiency. In these disorders the bone marrow stem cells are targeted for the introduction of the 'normal' gene so that a continuous source of 'normal' cells is provided. Genes packaged in liposomes bearing receptors for hepatocytes are also being investigated — the new DNA integrates into the hepatocyte genome. Alternatively, these gene-impregnated hepatocytes can be implanted into the peritoneum mixed with a supporting

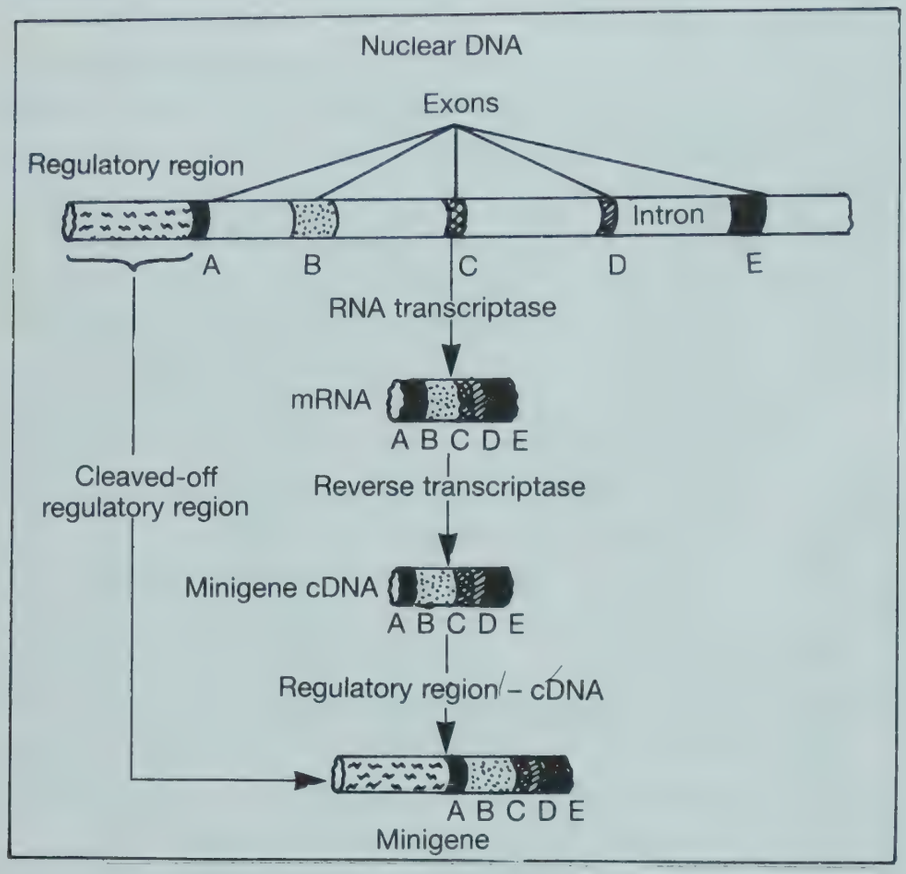


Fig 3.17a Gene therapy: ordinary (nuclear) genes are too large for insertion into cells and must therefore be converted into 'minigenes'. The first step is the production of mRNA. The messenger includes all the exons of the genes: it does not incorporate introns which account for most of the DNA of the nuclear genes. The mRNA, in turn, serves as a template for construction of complementary DNA (cDNA). The cDNA is combined with the regulatory region of the nuclear gene. The resulting minigene can be inserted into cells and may be expressed there.

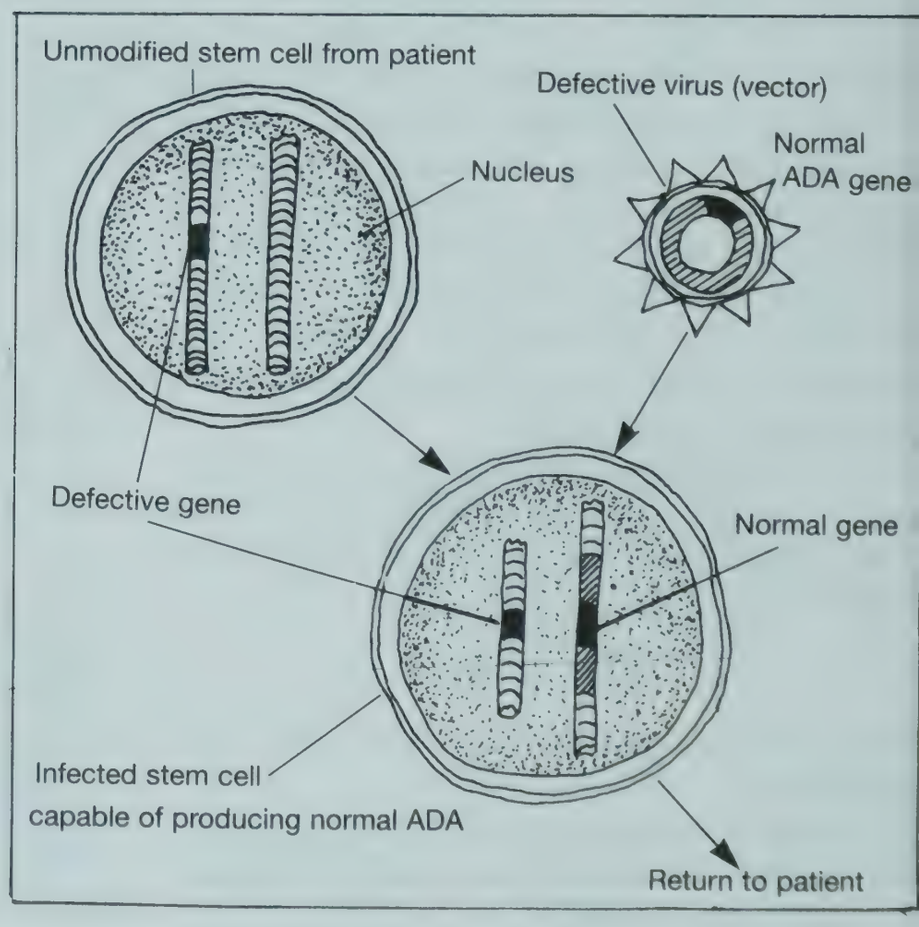


Fig 3.17b Gene therapy: gene insertion into lymphocytes, as in the correction of ADA deficiency, is fairly simple in principle. Stem cells are extracted from the patient's bone marrow and a normal ADA gene is inserted by means of a viral vector. The normalised cells are then injected into the circulation and migrate back to the bone marrow. The treated stem cells can then be expected to differentiate into normal lymphocytes.

connective tissue structure consisting of synthetic Goretex fibres, collagen and heparin binding growth factor-1. This admixture is called an *organoid* and is capable of secreting substances into the circulation. Similarly, skin and endothelial patches can be tailor-made to secrete insulin or tissue plasminogen activator into the circulation.

GENETICS OF CANCER: THE ONCOGENES

During the last decade, numerous important observations have improved our understanding of the pathobiology of carcinogenesis. These include the discovery of genes and genetic aberrations important in malignant transformation and the genetic regulation of cellular growth and differentiation.

Oncogenes

Oncogenes were discovered in the course of the study of the molecular biology of *retroviruses.*[1] These retroviruses which can cause tumours in mice, rats, cats and chicken, were found to contain certain genes involved in conveying the property of unlimited growth so characteristic of malignancy. These are the *oncogenes.* However, further study revealed that, surprisingly, the RNA derived from oncogenes was quite similar to that present in the cells of all mammals, including humans. The sequence of the base pairs of oncogenes has been remarkably conserved throughout evolution, suggesting a vital and universal role for their gene products. For the purpose of nomenclature, however, these genes are often named using three-letter abbreviations of the retrovirus from which they were first isolated — for example, *ras* from rat sarcoma (associated with a majority of human solid tumours), *src* from Rous sarcoma virus, *abl* from Abelson's leukemia virus and *myc* from avian myelocytomatosis virus.

[1] So called because they contain RNA and have to go back a step to DNA (using the enzyme reverse transcriptase) before they can divide

The term *proto-oncogene* is used for a normal cellular gene involved in the control of cellular proliferation and differentiation. Under certain circumstances these may be inordinately activated and transformed into 'oncogenes'.

Oncogenes are classified into four types, based on the nature of their products (Table 3.4, Fig 3.18). Thus, certain oncogenes code for *growth factors.* The autocrine production of these factors due to the activated corresponding oncogenes unleashes excessive uncontrolled growth. Thus, excessive expression of interleukin 2 has been reported to play a role in T cell lymphomas. Similarly, the striking homology between the *V-sis* oncogene and the platelet-derived growth factor B-chain (PDGF-B) gene may explain how the V-sis oncogene may cause unlimited growth.

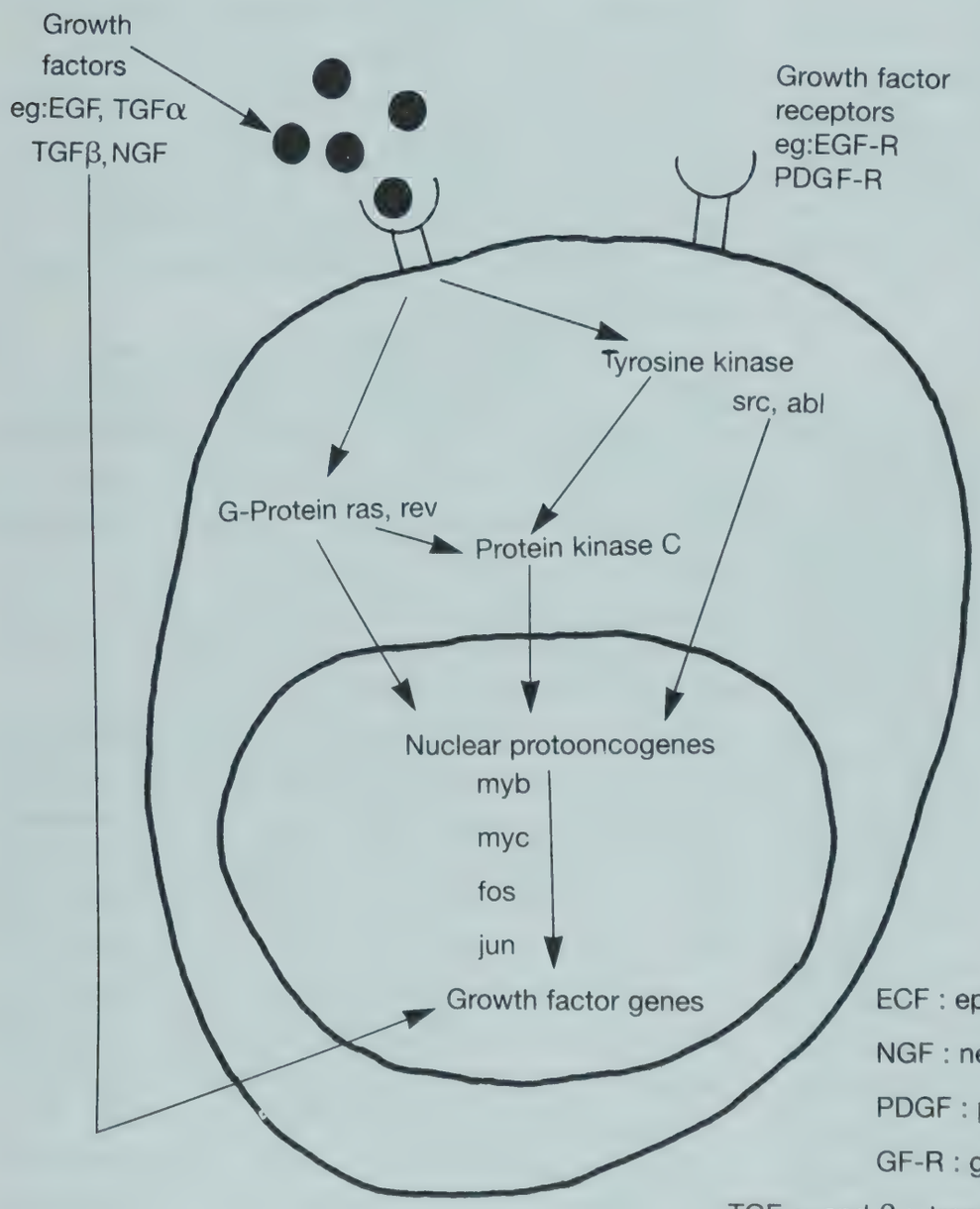
Certain other proto-oncogenes code for growth factor receptors. Specific mutations in these genes can result in their over-expression and result in a continuous stimulatory signal to the nucleus, causing excess growth. One such gene *C-erb-2* (also called c-neu) codes for a transmembrane growth factor receptor (similar to the epidermal growth factor EGF receptor), and amplification of the C-erb B-2 gene is a useful marker for recurrence of breast cancer.

A third class of proteins encoded by the oncogenes is the *signal transduction proteins,* that is, proteins which transmit commands of hormones or substances from the cell surface to the interior of the cell. One such family of proteins identified as the 'tyrosine kinases' bind primarily to growth factors and insulin. Amplification of the tyrosine kinases can result, understandably, in uncontrolled growth. One such example is the role of the *C-abl* oncogene in the pathogenesis of chronic myeloid leukemia (CML). More than 90 per cent of CML cases have an abnormal *Philadelphia chromosome* resulting from a reciprocal translocation of chromosomes 9 and 22. This involves the translocation of the *C-abl* proto-oncogene from

chromosomes 9 to within a 5.8 kb[1] segment of DNA on chromosome 22 identified as the *breakpoint cluster region (bcr)*. This translocation results in a 210 kd[2] phosphoprotein (P 210) that has very high tyrosine kinase activity unlike the normal 145 kd *C-abl* gene product (Fig 3.19). This translocation is probably important in the pathogenesis of CML.

[1] kb : kilobases, a measure of weight of DNA
[2] kd : kilodaltons, a measure of molecular weight

The fourth class of oncogenes code fo *nuclear growth regulatory proteins.* Thus, th *C-myc* oncogene codes for a 60 kd DNA bindin phosphoprotein — its inhibition results i cellular differentiation (for example, myeloi differentiation of leukemic cells) while it overexpression prevents normal differentiatio Amplification of a *myc* gene has been noted i small-cell cancer of the lung and neuroblastoma and a *C-myc* translocation is a universal findin in Burkitt's lymphoma.



ECF : epidermal growth factor

NGF : nerve growth factor

PDGF : platelet derived growth factor

GF-R : growth factor receptor

TGF α and β : transforming growth factors (transform fibroblast proliferation from a type inhibited by contact with adjacent cells to a type not so inhibited). TGF inhibits lymphocyte proliferatio

Fig 3.18 Growth factors and oncogenes: signal transduction and growth regulation in eukaryotic cells. Representative proto-oncogenes in the signal transduction pathway have been noted.

Stepwise activation of oncogenes

There is considerable evidence to show that the *initiation* and *promotion* steps in the molecular process of carcinogenesis correspond to separate discrete mutagenic events, that is, activation of at least two sets of separate oncogenes. That has also been called the *two-hit hypothesis.*

Antioncogenes/Recessive Oncogenes

The study of hereditary tumours has identified certain other genes which regulate cellular growth and differentiation, that is, suppress oncogenesis, and hence these are called *antioncogenes.* One normal allele of these genes is adequate to protect against a tumour. When both copies are inactivated, tumours can occur.

Table 3.4 Classification of oncogenes

Oncogene product	Example	Associated tumour
1. Growth factors	EGF	
	IL	T cell lymphoma
	PDGF	sarcomas
2. Growth factor receptors	ERB-bl c-	
	ERB-b2 (neu)	breast cancer
	PDGF-r	
3. Signal transduction proteins		
protein kinases	abl	chronic myeloid leukemia
	src	sarcomas
	protein kinases	
G proteins	Ha, Ki, N-ras	solid tumours
4. Nuclear proteins	myc	Burkitt's lymphoma
	fos	osteosarcomas

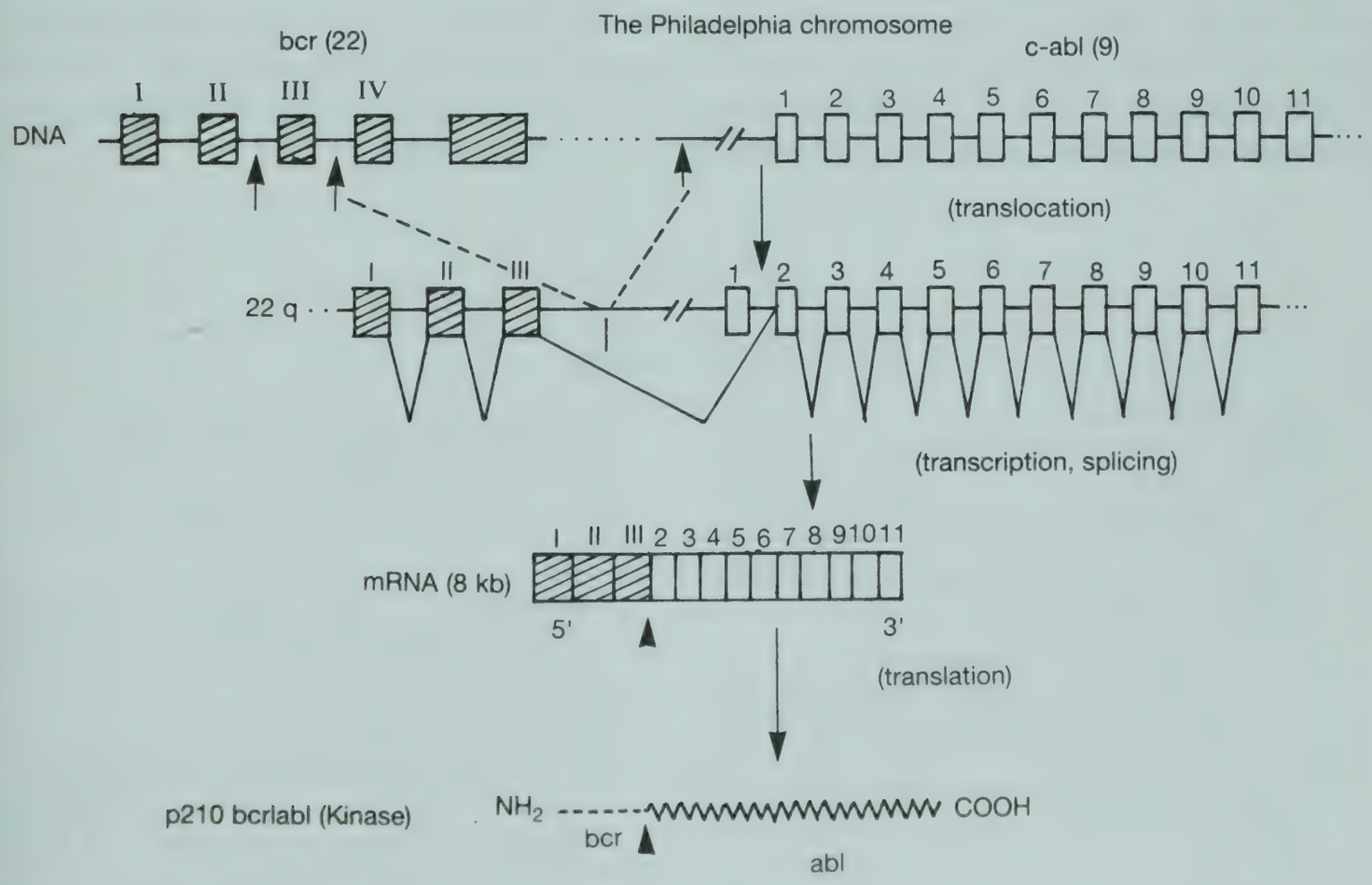


Fig 3.19 In molecular biology of chronic myeloid leukemia the t(9:22) translocation creates a fused bcr/c-abl gene. Arrows represent various breakpoints on chromosomes 9 and 22. Boxes represent exons, whose size and position are not drawn to scale. In the case illustrated the breakpoint on chromosome 22 is between bcr exons III and IV. c-abl information introns are deleted during transcription. The arrowhead indicates the junction between bcr and c-abl information in the mRNA and protein.

The first recessive antioncogene to be isolated was the retinoblastoma gene (Rb) located on the long arm of chromosome 13. Thus, deletions on chromosome 13 occurring in a homozygous fashion result in two inactive Rb genes, and a retinoblastoma develops. Similarly, Wilms' tumour requires homozygosity of a mutation for a deletion on chromosome 11, and thus, there would be two inactivated antioncogene copies (which have now been identified to code for a particular protein called a zinc-finger protein).

Tumour metastasis

The ability to metastasise is the hallmark of the biologic behaviour of malignant tumours. A number of investigators have identified genes which are specifically expressed in metastatic cells, whereas other workers have identified genes preferentially expressed in cells which do not have metastatic capabilities. Development of metastasis is, therefore, likely to be a complex interplay of genes coding for positive (metastasis enhancing) and negative (metastasis inhibiting) factors.

Prognostic and therapeutic applications The identification of specific oncogenes serves both prognostic and therapeutic purposes. Thus, the identification of 'n-myc' oncogenes in turn identifies a subset of neuroblastomas with the worst biological behaviour as well as with a high likelihood of chemotherapeutic drug resistance. Similarly monoclonal antibodies directed against the 'c-neu' oncogene can reverse the phenotypic changes in neuroblastoma cells. Mithramycin, a chemotherapeutic agent that selectively inhibits expression of the 'c-myc' oncogene, has been found to be useful in some patients with CML.

Thus, the techniques of modern molecular biology have led to a unifying concept of tumorigenesis with tremendous prospects for improved and more specific treatment of malignant disease in the years to come.

KEY CONCEPTS

- Genetic information is contained in nuclear DNA. DNA is a linear polymer of purine and pyrimidine bases. A gene is a sequence of DNA that encodes a single polypeptide. Information in the DNA is *transcribed* into messenger RNA which is then *translated* into the amino acid sequence of a protein by transfer RNA attached to ribosomes.
- There are 23 pairs of chromosomes. Genes are located at *loci* on chromosomes. Alternate forms of genes are *alleles*. Meiotic crossing over results in genetic recombination that enhances the diversity of the human genome. Gene loci that are close are said to be *linked*. A *mutation* is a stable heritable alteration in DNA.
- Inherited defects may be chromosomal (altered number or structure), Mendelian (single gene mutation), multifactorial or mitochondrial in origin.
- *Autosomal dominant*: vertical transmission; offspring : 50% affected; no sex predilection.

  Autosomal recessive: horizontal transmission; offspring : 25% affected, 50% carriers if both parents are carriers; no sex predilection.

  X-linked dominant: females more often affected; often lethal.

  X-linked recessive: oblique transmission; males do not transmit to sons, but all daughters are carriers. Male offspring of the carrier female has 50% chance of being affected.

  The genetic loci most strikingly associated with the disease are those of the HLA system on chromosome 6; at present clinical value is limited to: B-27 and ankylosing spondylitis, paternity testing, and genetic counselling in hemochromatosis.
- DNA can be analysed using several recombinant DNA techniques. These include molecular cloning, sequencing, nucleic acid hybridisation using allele-specific probes, Southern blotting, and the PCR. PCR is a technique for DNA amplification.

- Polymorphic markers on DNA permit identification of genetic mutations.
- Strategies for preventing genetic diseases include: genetic screening, genetic counselling and prenatal diagnosis. Prenatal screening is feasible using amniocentesis, chorionic villus sampling, maternal serum sampling and by fetal sonography.
- Gene therapy is an evolving area involving delivery of genes integrated into vectors and liposomes. Potential applications presently include cystic fibrosis, α_1 antitrypsin deficiency, adenosine deaminase deficiency.
- *Oncogenes* are genes that normally code for growth factors, receptors and signal transduction molecules. They can cause malignant transformation of cells when inappropriately expressed (mutation, amplification, rearrangement).

4

Clinical Pharmacology

BASIC PRINCIPLES

Clinical pharmacology is the scientific study of drugs in humans. It comprises two broad divisions: 1) *pharmacokinetics*, the study of the absorption, distribution, metabolism and elimination of drugs (that is, what the body does to the drug), and 2) *pharmacodynamics*, the study of the effects of drugs and the inherent mechanisms of those effects (that is, what the drug does to the body).

Time course of drug concentrations: order of the reaction For most clinically used drugs, the rates of absorption, distribution and elimination vary in direct proportion to the concentration of the drug.[1] Simply put, the rate of movement across cell membranes is high at high concentrations and low at low concentrations.

$$R(\text{abs, elim}) \propto C^1(\text{conc})$$

that is, the reaction follows *first order kinetics*.

There are other drugs (alcohol, phenytoin, salicylates, theophylline) which have a rate of absorption and elimination not proportional to the dose of the drug. These drugs are said to have *zero order* or *saturation kinetics*. Enzyme limited metabolic reactions show this 'rate limitation', as the amount of enzyme present is finite.

[1] Follows from the 'law of mass action' which states that the rate of a reaction is proportional to the active mass of the reacting substances

Mathematically speaking, for zero order kinetics,[2]

$$R(\text{abs, elim}) \propto C^0(\text{conc})$$

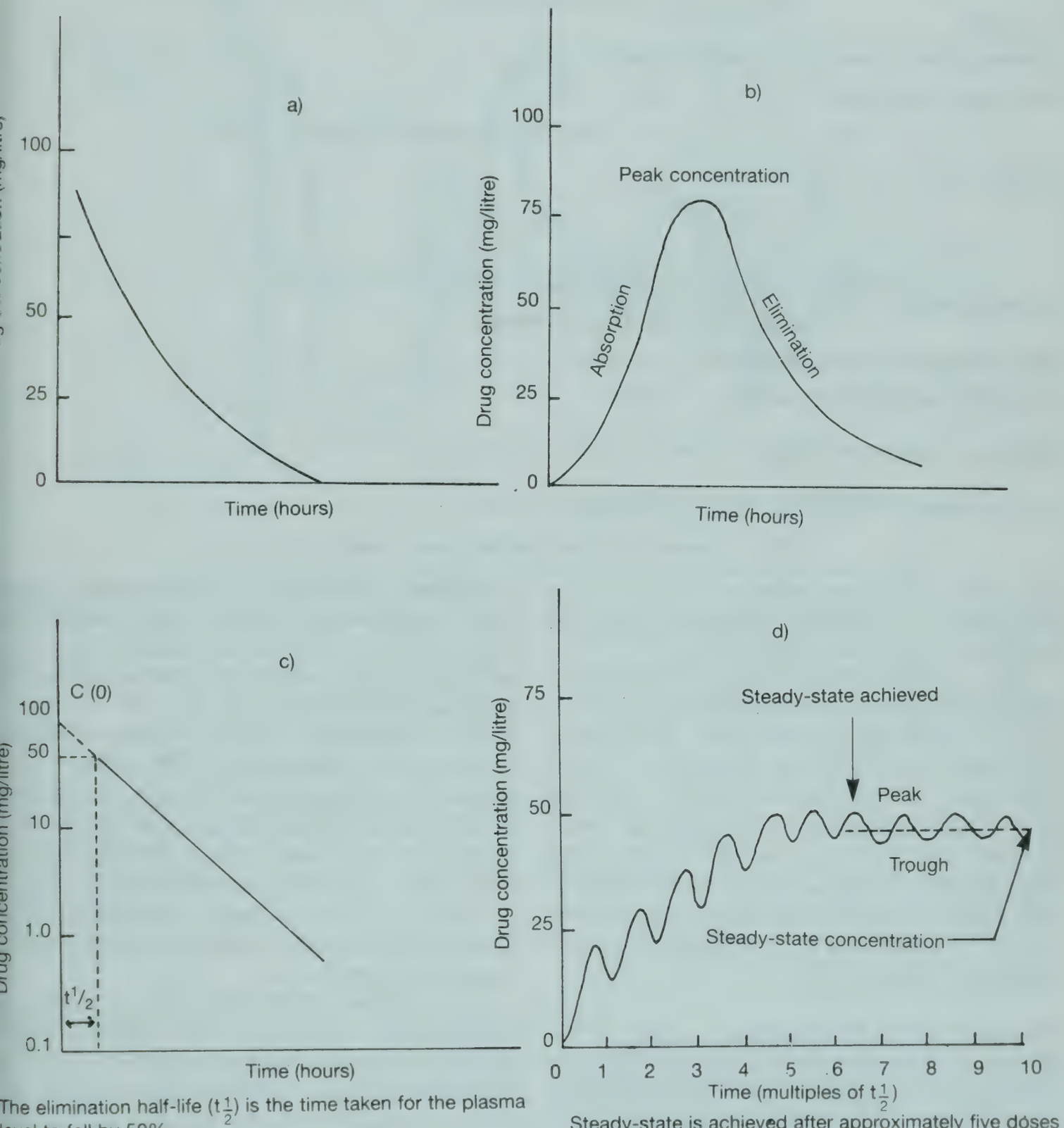
that is, the rate of reaction is independent of the concentration.

Plasma half-life ($T^1/_2$) For drugs with first order kinetics, the time taken for any plasma concentration to fall by 50 per cent is constant and is called the *plasma half-life* ($T^1/_2$). It can be used to predict the time to achieve 'steady state' levels after starting the drug as well as the time to eliminate most of the drug after stopping it. About four half-lives are usually required for plasma levels to achieve a plateau (as well as for the drug to be eliminated) (Fig 4.1).

When the plasma half-life of a drug is very short, a continuous intravenous infusion of the drug is required (for example, for dobutamine, $T^1/_2$ is two minutes). When the half-life of a drug is 6–12 hours, replacing the drug at intervals equal to the $T^1/_2$ suffices. When the half-life of a drug is 6–12 hours, the daily dose is the amount of drug which is eliminated in 24 hours, a value that can be calculated from the initial dose, plasma half-life, and the dose interval (Fig 4.2).

Dose dependent pharmacokinetics For some drugs, the amount of drug eliminated is not directly related to the drug concentration.

[2] The order of a reaction is the sum of the concentration term appearing in the equation relating the rate of the reaction and the concentration.



The elimination half-life ($t\frac{1}{2}$) is the time taken for the plasma level to fall by 50%

C (0) is the extrapolated concentration at the time of injection.

Steady-state is achieved after approximately five doses

Fig 4.1 a Plasma concentration-time curve following a single intravenous dose
b Plasma concentration-time curve following a single oral dose
c Log-linear plot of a concentration-time curve following an intravenous dose
d Plasma concentration profile of a drug given chronically at half-life intervals

Loading dose or initial dose D_i ——— D_t + eliminated drug
't' hours

Therefore, after 't' hours, D_i-D_t must be replaced.

Maintenance dose (D_m) = $D_i - D_t$

$D_t = D_i \cdot e^{-kt}$ where k = elimination constant = $0.693 / t^1/_2$

Therefore, $D_m = D_i (1 - e^{-kt})$

$$= D_i \left(1 - e^{\frac{-0.693t}{t^1/_2}}\right) *$$

$$\text{Loading dose } (D_i) = \frac{100 \times \text{maintenance dose}}{\% \text{ drug eliminated per dosage interval}}$$

Thus, for digoxin, maintenance dose = 0.25 mg

% drug eliminated per 24 hours = 35%

$$\text{Therefore, loading dose of digoxin} = \frac{100 \times 0.25}{35} = 0.75 \text{ mg}$$

* can be calculated using a calculator with an 'e' (natural logarithm) function

Fig 4.2 Calculation of maintenance dose and loading dose

In fact, as the concentration of the drug is increased, its clearance decreases (due to saturation of the elimination system).

Thus, with phenytoin a dose of 300 mg per day may give rise to plasma levels of 8 μg/ml, but a dose of 400 mg per day may give rise to dangerous levels of 35 μg/ml or more. Conversely, in phenytoin toxicity the half-life may be more than three days but as the levels decrease, the $T^1/_2$ drops to 20–30 hours. The drug also shows interpatient variability, so that both plasma levels and the clinical picture may have to be considered for establishing a proper maintenance dose.

Sustained release preparations The dosing interval of a drug with a short half-life (and hence requiring multiple doses) can be reduced by using these 'slow release preparations'.

These preparations have various drug coatings—plastic matrices, resins, chelates or formulations—from which the egress of drugs is controlled osmotically. When the frequency of administration is reduced, intake of the drug is more convenient and there is better compliance.

Presystemic elimination or the first-pass effec When administered orally, a drug reaches the liver through the portal circulation, where i undergoes hepatic elimination before it reache the systemic circulation (Fig 4.3).

This is referred to as the *first-pass* effect o presystemic elimination. For drugs lik morphine and lignocaine, this may be so hig as to preclude oral administration. Drugs wit significant first-pass effect include som ß-blockers (propranolol, metoprolol), nitro glycerin and propoxyphene. Other drugs lik diazepam, phenytoin, warfarin have negligibl presystemic elimination.

The parenteral (intravenous, intramuscular o subcutaneous injection), sublingual, trans bronchial, intranasal and transdermal routes o administration have the advantage of deliverin the drug directly into the systemic circulatio thus avoiding a first-pass effect.

Therapeutic level monitoring

Because drug disposition as well as tissue re ponsiveness show inter-individual variation different doses of the same drug may be require

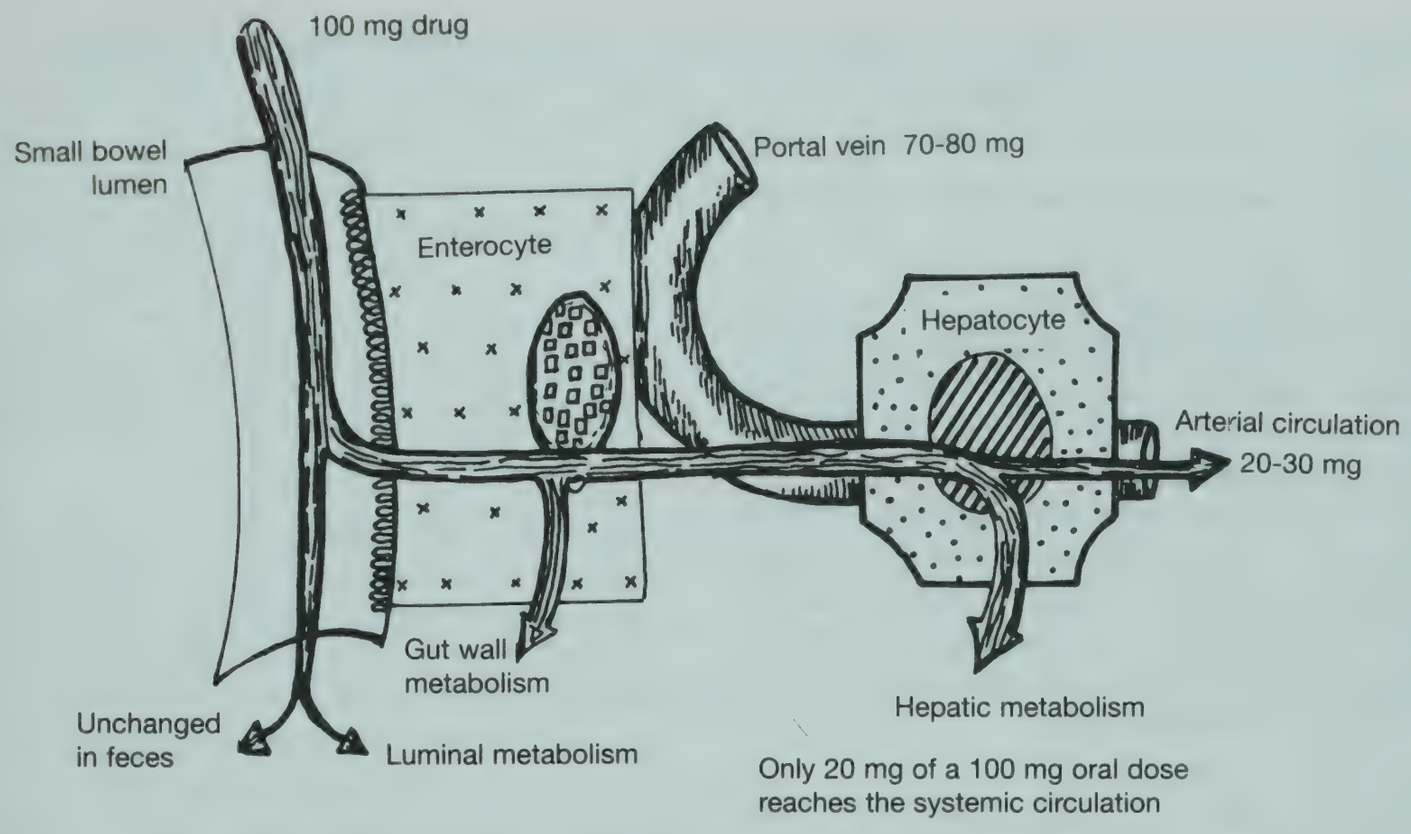


Fig 4.3 First-pass metabolism of a drug metabolised substantially in the gut wall and liver

in different individuals for attaining the same effective therapeutic plasma concentrations. This has led to the concept of monitoring drug levels to optimise therapeutic effects and to minimise toxic effects. However, plasma concentration monitoring is not useful if:

1. there is a quicker, more easily determined method of assessing drug effect, for example, body weight for diuretics, blood pressure for antihypertensives, blood sugar for antidiabetic agents;
2. the end point of drug therapy is itself not too finitely defined;
3. *the therapeutic index*[1] itself is wide;
4. the drug has active metabolites (for example, procainamide is metabolised to N-acetyl-procainamide—NAPA) or the concentration of the drug at the receptor level is not reflected by its concentration in plasma.

Therapeutic monitoring of drug levels is indicated especially for drugs with a narrow therapeutic ratio (for example, lithium, digoxin) or drugs which show dose-dependent kinetics (for example, phenytoin, theophylline). They are also useful to confirm the possibility of non-compliance and to confirm overdose.

The best time for drawing blood for drug assays depends on the half-life of the drug. All drug assays must be made after a steady state is reached (that is, more than four half-lives have elapsed after starting therapy). For drugs given once daily, the best time is at least eight hours after the last oral dose. For shorter acting drugs, both peak (15 minutes after i.v. dosage) and trough levels (just before the next dose) are measured. The therapeutic range of common drugs (which are monitored) is shown in Table 4.1.

Table 4.1 Therapeutic levels of some drugs

Drug	*Therapeutic range*	*Toxic effect*
Phenytoin	10–20 mg/litre*	25 mg/litre
Theophylline	10–20 mg/litre	25 mg/litre
Digoxin	0.8–2 μg/litre**	3 μg/litre
Lithium	0.5–1.5 mEq/litre	1.5 mEq/litre
Carbamazepine	4 mg/litre***	10 mg/litre

* Equal to 20 μg/ml
** Equal to 0.8 ng/ml
*** Equal to 17 μmol/litre

[1] The therapeutic index is toxic dose/therapeutic dose.

DRUG DOSING IN DISEASE STATES AND SPECIAL GROUPS

Drug Dosing in Renal disease (Tables 4.2, 4.3)

Loading dose Usually in renal failure, the initial or loading dose does not change as it depends on the volume in which the drug has to distribute (and this should not alter in renal failure). However, the protein binding of drugs can be altered due to the hypoproteinemia that may be associated with renal failure, thereby increasing the unbound (active) drug concentration. Hence it may be wise to initiate therapy at a less than normal dose if the drug is markedly protein bound and there is associated significant hypoproteinemia.

Maintenance dose Drugs can be broadly divided into three categories based on their renal excretion (Table 4.2). Thus, drugs that are wholly metabolised and therefore have insignificant renal excretion can be administered without a change in dosage in renal failure. There are other drugs with dominantly renal excretion and insignificant non-renal excretion. The clearance of these drugs varies in direct proportion to the creatinine clearance. If the creatinine clearance is halved, the drug clearance is halved ($T^1/_2$ would be doubled). There are two ways to alter the schedule of these drugs in renal failure.

1. Change the dosing interval (DI), thus:

$$DI_{RF} = DI_N \times \frac{CC_{r_N}}{CC_{r_{RF}}}$$

where N = normal,
RF = renal failure,
CC = creatinine clearance

Thus, if the normal dosing interval is 8 hours and creatinine clearance is 50 ml/minute the normal dose of the drug is repeated every 16 hours.

2. Alter the dose without changing the dosing interval. Thus if the normal dose of gentamycin is 5 mg/kg i.v. every eight hours and creatinne clearance is 20 ml/minute, the dose can be changed to 1.0 mg/kg i.v. every eight hours.

In patients on dialysis, the dialysability of the drug and frequency of dialysis need to be considered in calculating the clearance. Doses are usually administered soon after each dialysis. For drugs that have significant renal and non-renal clearance, the calculation is more complex and is shown in Fig 4.4.

Drug dosing in liver disease (Table 4.3) Liver disease also alters the pharmacokinetics of metabolised drugs due to a combination of reduced capacity for drug metabolism (decreased hepatocyte function), bypassing of the hepatocyte machinery (due to portal systemic shunts in cirrhosis) and due to altered protein binding (due to hypoalbuminemia).

Table 4.2 Drugs and renal elimination

Drugs eliminated exclusively by the kidneys			*Drugs partly metabolised and partly eliminated by the kidneys*			*Drugs entirely metabolised*		
		$T^1/_2$ (hr)			$T^1/_2$ (hr)			$T^1/_2$ (hr)
Drug	**N**	**ESRD***	**Drug**	**N**	**ESRD**	**Drug**	**N**	**= ESRD**
Penicillin	0.5	8	Digoxin	36	120	Rifampicin		3
Ampicillin	1	14	Trimethoprim	10	25	Propranolol		3
Acyclovir	2.5	20	Chlorpropamide	36	200	Warfarin		40
Gentamycin	2.5	50				Doxycycline		18
Sotalol	5	40				Paracetamol		2
Atenolol	6	100						

* ESRD – end stage renal disease, i.e, creatinine clearance < 5 ml/min; N – normal renal function

$$Dose_{RF} = Dose_N \times \frac{Cl_{RF}}{Cl_N}$$

$$Cl_N = Cl_R + Cl_{NR}$$

$$Cl_{RF} = Cl_R + Cl_{NR}$$

where Cl = clearance of drug
RF = renal failure
N = normal

where R = renal
NR = non-renal

$$= Cl_R \times \frac{CC_{r_{RF}}}{CC_{r_N}} + Cl_{NR}$$

(as renal clearance of drug is reduced proportional to reduction in creatinine clearance)

$$= \frac{Cl_R \times CC_{r_{RF}}}{100} + Cl_{NR}$$

(assuming normal CC_r of 100 ml/minute)

1. If Cl_R is negligible, no alteration of dose is required.
2. If Cl_{NR} is not negligible, calculate as per formula above, for example, for digoxin,

$$Cl_N = Cl_R + Cl_{NR}$$
$$= 110 \text{ ml/minute} + 40 \text{ ml/minute}$$
$$= 150 \text{ ml/minute}$$

$$Cl_{RF} = Cl_R \times \frac{CC_{r_{RF}}}{100} + 40$$

If CC_r is 25 ml/minute,

$$Cl_{RF} = \frac{110 \times 25}{100} + 40 = 67.5 \text{ ml/minute}$$

$$Dose_{RF} = Dose_N \times \frac{67.5}{150} = 0.25 \text{ mg} \times \frac{67.5}{150} = 0.11$$

or $^1/_2$ of the normal dose (approx)

Fig 4.4 Calculation of drug dose in renal failure

However, there are no quantitative guidelines for altering drug dosage in liver disease.

DRUG INTERACTIONS

Drug interaction is the modification (enhancement, diminution or elimination) of the expected actions of a drug by another drug or chemical (called the *interactant*). It may also result in new effects not seen with either of the drugs alone. The definition implies interactions within the body, so that physical and chemical incompatibilities are excluded.

General principles Drug interactions are ubiquitous, yet only occasionally do they have clinical importance. This is because many drugs have large therapeutic indices; moderate

Table 4.3 Drug prescription in renal and hepatic disease

Class of drugs	*Renal disease*		*Hepatic disease*	
	safe	*avoid/alter dose*	*safe*	*avoid/alter dose*
Analgesics	methadone naloxone	morphine (effect increases) pethidine (risk of seizures) codeine	pethidine	other opioids
NSAIDs	paracetamol tolmetin sulindac	most NSAIDs	most NSAIDs	naproxen paracetamol ibuprofen aspirin
Anticonvulsants	phenytoin sodium valproate carbamazepine			phenobarbitone sodium valproate carbamazepine phenytoin
Antidiabetics	glipizide insulin	chlorpropamide metformin	tolbutamide phenformin	chlorpropamide
Antibiotics	penicillins doxycycline chloramphenicol	aminoglycoside (reduce dose) sulphonamide tetracycline	gentamicin penicillins streptomycin ethambutol	sulphonamides rifampicin INH (reduce dose) ampicillin esters tetracycline
CVS drugs	propranolol metoprolol nifedipine lignocaine M dopa frusemide heparin warfarin	acebutalol atenolol captopril enalapril procainanide (reduce dose) disopyramide thiazide (ineffective if CC_r is less than 20 ml/min)	atenolol nifedipine captopril frusemide heparin warfarin	propranolol lignocaine mexilitene (reduce dose) tocainide M dopa thiazides amiodarone
Psychoactive drugs	diazepam chlorpromazine	lithium	oxazepam lorazepam	chlorpromazine

increases in drug concentration may not manifest as toxicity. Other drugs are given without well-defined therapeutic endpoints, making both the drug effect and the change in drug effect (due to interaction) difficult to assess. Also the disease being treated may not be serious enough for a slight decrease in drug concentration to be easily recognised. Thus drug interactions are likely to be recognised if 1) the drugs have an easily recognised toxicity a well as a low therapeutic index, for exampl anticoagulants, oral hypoglycemic agent 2) a decrease in drug levels leads to disea breakthrough, for example, anticonvulsant antiarrhythmics, corticosteroids; 3) therapeut endpoints are easily quantifiable, for exampl blood sugar (for oral hypoglycemic) ar prothrombin time (for oral anticoagulants).

Drug interactions are also more likely in the *elderly*, in patients receiving *polypharmacy*, in patients with complicated acute *severe* illness and in patients with an *unstable* clinical illness (for example, brittle diabetes). Broadly speaking, drug interactions are of two types:

1. *Pharmacokinetic interactions* take place during the absorption, distribution, metabolism or excretion of the drug.
2. *Pharmacodynamic interactions* result in a change in drug effect without altering the amount of drug available at the site of action.

Pharmacokinetic Interactions

Interactions during absorption

A change in drug absorption may occur by one of the following means.

Intraluminal complexing Antacids containing divalent and trivalent cations form insoluble complexes wth tetracyclines, iron and prednisolone. Cholestyramine (an anion exchange resin with a high affinity for acidic molecules) impairs absorption of warfarin, digitoxin, aspirin, thyroxine and phenylbutazone. Mineral oils in laxatives sequester vitamins A, D and K. Kaolin-pectin preparations bind digoxin, thereby decreasing the amount absorbed. These interactions can be avoided by separating the intake of the two drugs by approximately two hours.

Altering gastric transit time The rate of absorption of a drug which is mainly absorbed in the intestines is enhanced by drugs which hasten gastric emptying (for example, metoclopramide) and is diminished by drugs which retard gastric emptying (opioids, propantheline). For a drug which is absorbed in the stomach, the effects of these agents would be the opposite. Usually since the small intestine has a large absorptive area, the amount of drug absorbed is not affected but the rate of onset of action is affected. If a drug is inactivated in acid pH (for example L dopa, penicillin), then a delay in gastric emptying can lead to inactivation of the drug.

Change of pH in the stomach/intestine Most of the drugs are weak acids or bases and are best absorbed through the gastric/intestinal mucosa in the non-ionised lipid soluble form. A change in gastric/intestinal pH can therefore affect drug solubility and absorption. Thus, cimetidine increases gastric pH and if given with ketoconazole can reduce the absorption of the latter by 65 per cent.

Change in gut flora Changes in the gastrointestinal bacterical flora can lead to altered drug metabolism. Thus, estrogens in oral contraceptives are conjugated by the liver, excreted in the bile and then deconjugated by bacterial β glucoronidases to the parent steroid, which is reabsorbed (enterohepatic circulation). Therefore, elimination of bacterial flora by antibiotics can lead to a diminished efficacy of oral contraceptives.

Interactions during drug distribution

Changes in plasma protein binding Many drugs, especially acidic ones, are transported in blood, bound to albumin. The unbound or free fraction is in equilibrium with the plasma protein bound fraction and the tissue stores. This free (unbound) fraction undergoes renal clearance. Displacement of a drug from plasma proteins by another drug usually results in only transient effects as the increased free fraction is also subjected to increased renal clearance. A protein binding displacement interaction is noticeable if the drug is *highly protein bound* (> 90%), has a *small distribution volume* and a *narrow therapeutic index*. Some clinical interactions arise because of dual mechanism; hepatic enzyme inhibition (discussed later) and protein binding displacement occur together, for example, phenylbutazone potentiates warfarin and sodium valproate precipitates phenytoin toxicity.

Change in transmembrane transport Antihypertensive drugs like bethanidine and debrisoquin act after being taken up into

adrenergic neurons at neuronal terminals. Tricyclic antidepressants, high dose phenothiazines and some antihistamines block this neuronal uptake and cause a hypertensive response in patients otherwise well-controlled on these antihypertensive drugs.

Interactions due to altered drug metabolism

Enzyme induction Some drugs bind to cytosolic receptors in the hepatic endoplasmic reticulum to activate the production of the *mixed function oxygenase enzyme system* (contained within a system called *cytochrome* P_{450} system). As this effect requires protein synthesis, it may require 2–3 weeks to become manifest. The clinical result is an increased metabolism of a number of lipid soluble drugs, with an attenuation of their pharmacological effects, for example, rifampicin, phenobarbitone, phenytoin and carbamazepine are inducers of hepatic enzymes. Thus barbiturates may attenuate the effect of oral anticoagulants, and smokers require higher doses of theophylline.

Enzyme inhibition Many drugs inhibit the hepatic microsomal enzymes and thus can potentiate the effects of drugs which are inactivated by these enzymes, for example, amiodarone, cimetidine, verapamil, erythromycin, metronidazole and allopurinol.

Change in cofactors L dopa is peripherally decarboxylated by the enzyme DOPA decarboxylase, pyridoxine being a cofactor in the reaction. The result is that < 1% of the drug enters the central nervous system. Pharmacologic doses of pyridoxine can further increase the peripheral metabolism, decreasing even further the amount of drug entering the central nervous system.

Competition for enzyme/cosubstrate Isonazid and phenytoin compete for acetylation, so that a combination therapy leads to increased serum levels of phenytoin, with a consequent risk of phenytoin toxicity. This is more likely in slow acetylators especially during the phase of initiating isoniazid therapy.

Interactions due to altered excretion

In the kidneys, the amount of drug filtered at the glomerulus is directly proportional to the unbound drug concentration in plasma. Drugs are also actively secreted in the proximal convoluted tubules by two well-defined carrier systems, one for weak acids and one for weak bases. Thus, probenecid decreases penicillin excretion, and spironolactone and quinidine verapamil decrease digoxin excretion.

Interactions at the receptor level

A drug may interfere with the action of another drug at the receptor level by *competitive* or *non competitive inhibition* of receptors, for example antagonism of warfarin by vitamin K, of narcotics by naloxone, of dopamine by chlorpromazine, of clonidine by tricyclic antidepressants. Other interactions involve an *alteration of the sensitivity of the receptors,* for example, potentiation of the effect of oral anticoagulants by clofibrate and anabolic steroids.

Pharmacodynamic Interactions

These include the interaction of oral anticoagulants with antiplatelet drugs and heparin (increasing bleeding risk), neuromuscular blockers with aminoglycosides (increasing paralysis), β-blockers with disopyramide (increasing negative inotropy) and furosemide with aminoglycosides (increased ototoxicity).

Thus drug interactions are complex and often not predictable with mathematical accuracy, and show *inter-individual variability.* Their importance lies in the awareness of their existence, taking a complete drug history especially when dealing with the use of multiple drugs (with low therapeutic indices) in a patient with a serious illness with multisystem involvement.

KEY CONCEPTS

- After administration, a drug is *absorbed, distributed*, and then *eliminated*. An orally administered drug may be metabolised in the gut wall and in the liver even before it has entered the circulation (*first-pass metabolism*).
- Plasma levels of a drug depend on the volume of distribution. Binding to plasma proteins influences the distribution of a drug. This is important as only the unbound or *free* form of the drug is available for diffusion to tissue sites where it is active.
- Most drugs are eliminated by *first order kinetics*. The $T^1/_2$ (the time for plasma levels to decrease to 50%) of a drug identifies the time to steady state and is a measure of the rate of elimination. The $T^1/_2$ depends on the volume of distribution and the clearance rate.
- Most drugs are given at $T^1/_2$ intervals. Four $T^1/_2$ are required for steady state levels. *Loading* doses are used to accelerate onset to steady state. Controlled-release forms are used to reduce the frequency of dosage, maintain steady state and to ensure compliance by facilitating patient convenience.
- *Serum levels* can be assayed if clinical indicators of drug efficacy are unreliable and the drug has a narrow therapeutic window.
- Drugs are eliminated principally by the kidneys (water soluble molecules) and liver (drugs and metabolites). The dose may accordingly have to be modified in renal failure and in liver disease.

  Dose in renal insufficiency (D_{RI})=$dose_{normal} \times Clearance_{RI}/Clearance_{normal}$

  Enterohepatic recirculation refers to the biliary secretion of a drug followed by its reabsorption in the intestines.
- Drug *interactions* are especially of concern for drugs with potent effects which have a narrow safety margin and a steep dose-response curve. They may be *pharmacokinetic* or *pharmaco dynamic*. Pharmacokinetic interactions result from altered drug delivery to its site of action; mechanisms include altered absorption (altered gastric pH, gut motility, presence of food or com plexation), altered distribution (displacement from binding proteins), and altered elimination (induction or suppression of hepatic enzymes, altered urine pH or tubular secretion). Pharmacodynamic interactions modify the response at target organ level by an effect at receptor and non-receptor sites.

5

Nutrition-related Disorders

Nutrition is the 'science of foods, nutrients and other substances therein, their action, interaction and balance in relationship to health and disease'.

Nutrients are the constituents in food that must be supplied to the body in suitable amounts for it to grow and remain healthy. These include water, proteins, fats and fatty acids, and carbohydrates (*macronutrients*) as well as minerals and vitamins (*micronutrients*).

Nutritional status is the state of health of the individual with regard to the overall utilisation of the nutrients.

Nutrient balance refers to the difference between the intake of a nutrient and its requirement.

Malnutrition is a disturbance of the nutritional status resulting from a deficiency, excess or an imbalance of nutrients. It includes undernutrition and overnutrition.

BASIC METABOLISM

The body uses glucose as the preferred immediate source of energy, a gram of glucose yielding 4 kilocalories[1] of energy. Whereas in the normal 'fed' state all cells utilise glucose, there are some cells (the neurons, the renal medulla, all blood cells) which can use only glucose as fuel under all circumstances. Under conditions of 'glucose excess' some of the ingested glucose is converted to glycogen and stored (about 200 g in the liver, 300 g in the muscle) as readily available reserves. Further excess dietary carbohydrate is converted to triglycerides and stored in the adipose depot. Under conditions of 'glucose depletion' the body can generate glucose endogenously by breaking down glycogen (*glycogenolysis*) or by synthesising it anew (*gluconeogenesis*). Glucogenic amino acids[2] (from protein catabolism) or the 'glycerol backbone' of triglycerides constitute the raw materials for gluconeogenesis. Fatty acids (the main component of triglycerides), however, cannot be converted into glucose.

Fats are the main energy reserves of the body, each gram of fat providing about 9 kilocalories of energy. Dietary fats are absorbed and hydrolysed to free fatty acids in the capillaries, from where they are used directly by some tissues (skeletal and cardiac muscles) or stored in the adipose tissues. Under conditions of starvation, the free fatty acids and the ketone bodies (which form from the incomplete oxidation of free fatty acids) are the major fuel utilised by the brain and the body.

The *protein* compartment of the body is maintained by daily intake (there being no storage form of protein) and is essential for structural elements, replacement-repair of tissues, enzymes, antibodies and serum proteins. As mentioned above, under conditions of severe caloric depletion, the body can catabolise its own protein to provide energy.

[1] For conversion to kilojoules (unit of work) multiply by 4.2.

[2] Alanine and glutamine are glucogenic amino acids.

The metabolic response to *stress* involves an increase in proteolysis and lipolysis to support gluconeogenesis and ketogenesis. The peripheral muscle becomes resistant to insulin and serum glucose levels rise as does lactate production (due to preferential utilisation and deamination of branched chain amino acids[1] to pyruvate, the latter being used as an energy substrate).

The metabolic adaptation to *starvation* is characterised by a decreased turnover of protein, diminished ureagenesis and increased ketogenesis (*ketoadaptation*). The peripheral muscle loses resistance to insulin, and insulin secretion drops as a result of a fall in serum glucose levels. Body stores of fat and expendable protein are utilised and total energy expenditure drops.

ASSESSMENT OF NUTRITIONAL STATUS

Nutritional assessment is a tool to measure the nutritional status as reflected by changes in body composition and function (Fig 5.1). A thorough history, which includes the patient's daily diet and documents any significant weight loss, and a careful physical examination will help identify any nutritional imbalance. The clinician also uses some anthropometric[2] measurements and some biochemical indices to help him identify the precise nature of the nutritional disorder.

Weight for height is the most commonly used measure, with less than 80 per cent ideal body weight being taken as indicative of *undernutrition.* However, it has limited validity as an assessment tool as it can be increased or be normal in states of undernutrition associated with edema (kwashiorkor). The *triceps skinfold* is a double fold of skin (and the fat between it) on the posterior aspect of the non-dominant arm, measured with specially designed calipers at a point midway between the acromial process of the scapula and the olecranon process of the ulna. It is an indirect estimate of subcutaneous fat, is universally accessible in both men and

[1] Valine, leucine, isoleucine are branched chain amino acids.

[2] Anthropometry is the science which describes body composition through the measurement of its external morphology.

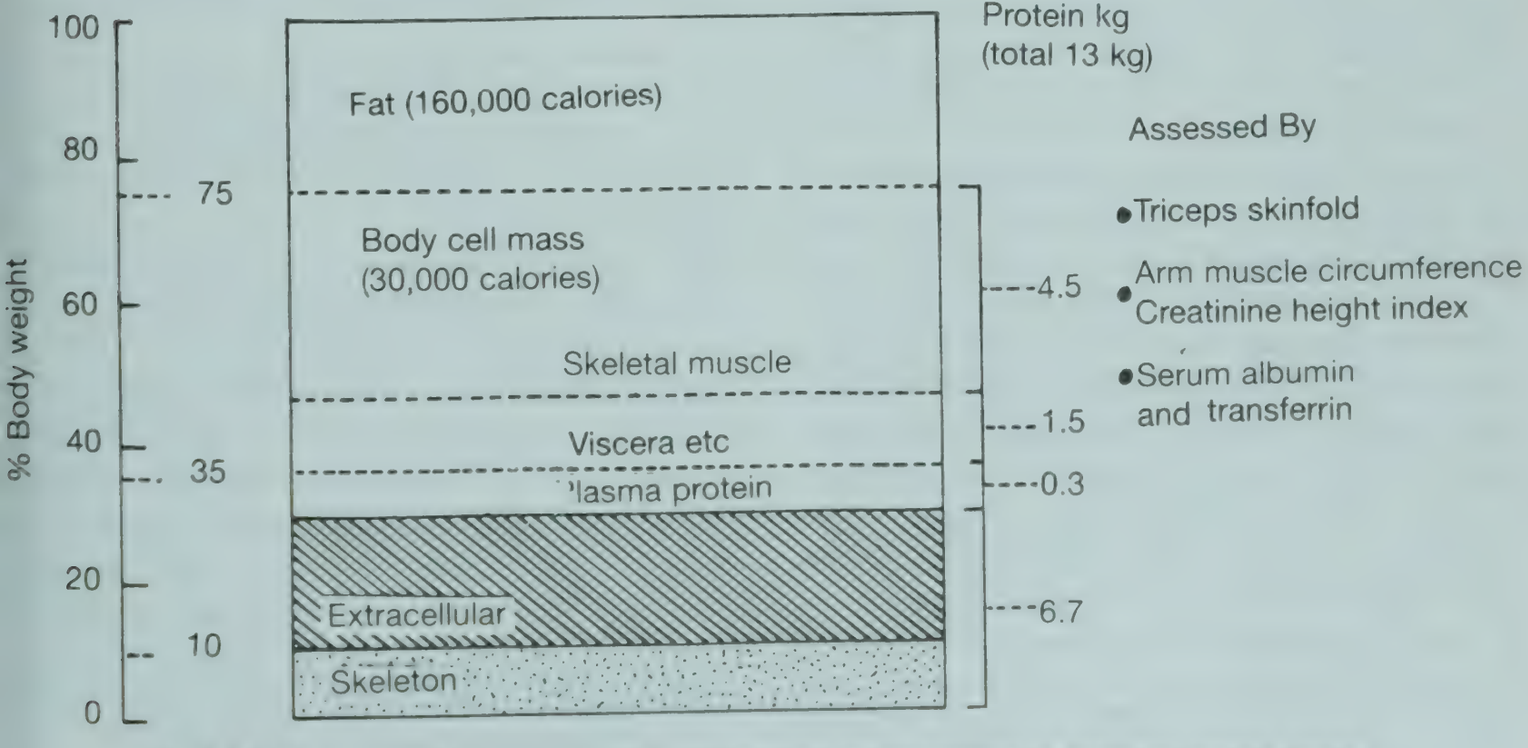


Fig 5.1 Body composition can be easily estimated by anthropometry or secretory protein levels

women and is unaffected by edema. Another measure used is the *mid-arm muscle circumference* (MAMC) that is derived mathematically using measurements of the mid-upper arm circumference (MAC) and the triceps skinfold (TSF) thus:

$$\text{MAMC (cm)} = \text{MAC (cm)} - \frac{\pi \times \text{TSF(mm)}}{10}$$

It is a measure of somatic protein muscle mass. Another alternate measure is the *body mass index*. This measure of body adiposity assumes that the weight, once it is corrected for height, is positively corrected to the body fat. The *Quatelet index* is one such index, defined thus:

$$\text{Quatelet index} = \frac{\text{weight (kg)}}{[\text{height (cm)}]^2} \times 100$$

The interpretations of anthropometric measurements is done by comparing them to standards derived from a reference population, a value in the range of 5–15 per cent of the standard being classified as moderate depletion, and less than five per cent of the standard as severe depletion.

There are several biochemical indices used to assess the nutritional status. The *creatinine–height index* (*CHI*) is used to assess skeletal muscle mass and requires estimation of the 24-hour urinary creatinine excretion. Creatinine is a secretory protein from the muscle formed at a constant rate in proportion to the amount of lean body mass and would be lower in a protein depleted individual, a CHI less than 75 per cent reflecting moderate malnutrition. However, errors in urine collection, the presence of renal disease and ascites can render the creatinine-height index an inaccurate measure of lean body mass. The ability to synthesise other secretory proteins such as serum albumin, prealbumin, transferrin and the retinol binding protein has been utilised to assess the functional capacity of the visceral compartment. *Transferrin* with a short half-life (8–10 days) seems to be a better index than albumin (half-life 20 days), allowing the detection of shorter periods of malnourishment. Serum transferrin values fall with malnutrition, reflecting a decreased synthesis by the hepatocytes (serum levels less than 170 mg/d are abnormal).

The *delayed hypersensitivity reaction* to intradermal injections of common recall antigens (such as tuberculin) and the *total lymphocyte* count have been used as reflectors of the state of cellular immune responses. In protein-deficient states, there may be *anergy*[1] and *lymphopenia* (<1500 lymphocytes/mm^3).

An ideal tool for nutritional assessment must be 1) highly sensitive (few false negatives) 2) highly specific (few false positives) 3) nutrition sensitive (normalising with repletion), and 4) nutrition specific (unaffected by factors other than nutrition). Since no single assessment tool meets all the criteria, a combination of parameters has been used to enhance the predictive value of the tools. One such combination developed is the *prognostic nutrition index* (*PNI*) which combines serum albumin, transferrin levels, with triceps skinfold measurement and delayed hypersensitivity responses to predict postoperative complications and mortality. Its accuracy has, however, turned out to be the subject of considerable controversy.

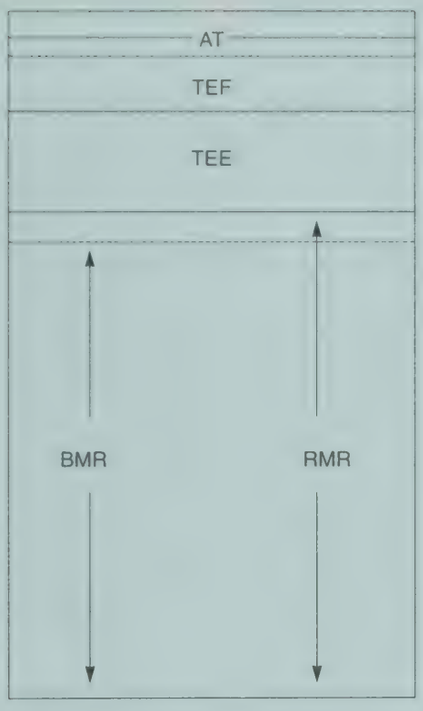
REQUIREMENTS FOR ENERGY AND MACRONUTRIENTS

Energy requirement

Three components of the requirement can be estimated for the healthy person (Fig 5.2).

1. The *basal metabolic rate* (*BMR*) is the rate of free heat production of an individual, measured by direct calorimetry in a neutral thermal environment when the individual is in a post prandial state for at least twelve hours. It is measured in an awake state with the individual relaxing. The central nervous system account

[1] Anergy is a state associated with non-responsiveness on skin testing, i.e., less than 5 mm induration measured at 24 and 48 hours after intradermal injection of tuberculin, Candida antigen or dinitrochlorobenzene.



AT : adaptive thermogenesis;
TEF : thermic effect of food;
TEE : thermic effect of exercise;
BMR : basal metabolic rate;
RMR : resting metabolic rate;

Fig 5.2 Twenty-four hour energy expenditure

for 18 per cent of the BMR, the circulatory-respiratory systems for 10 per cent, the rest of the body (chiefly skeletal muscles) utilises the remaining 72 per cent of the BMR. The BMR is influenced by age, sex and the lean body mass. Thus it is more for males and decreases by 1–2 per cent per decade with age, beyond the third decade. Another term used in this connection is the *resting energy expenditure* (*REE*). This is measured by calorimetry, ignoring the timing with respect to meals or the sleep pattern.

The basal metabolic rate can also be predicted using the *Harris Benedict equations* which require no tables and are reasonably accurate when compared to measurements of oxygen consumption.

BMR (for women) = $66.5 + 9.6 \times (W) + 1.8 \times (H) - 4.7 \times (A)$

(for men) = $66 + 13.7 \times (W) + 5 \times (H) - 6.8 \times (A)$

(where W is the actual weight in kg, H is the height in cm and A is the age in years.)

2. The *energy expenditure of activity* (*EAA*) is the daily energy requirement for day-to-day activities over and above the basal metabolic rate. Thus, it is 400–800 kcal/day for sedentary activity, 800–1200 kcal/day for light work, 1200–1800 kcal/day for moderately heavy work, and 1800–4000 kcal/day for strenuous labour.

3. The *thermic effect of food* (also known as *specific dynamic action*) refers to the additional energy required to metabolise and utilise ingested food and is usually about 10 per cent of the sum of BMR and EAA.

4. The *energy requirement during illness*: Febrile states are usually associated with an increased BMR (increased consumption due to fever), a decreased EAA (due to relative immobilisation) and a decrease in the thermic effect of food (decreased intake). Overall, therefore, there is a net increase in energy requirement which may be 10 per cent of BMR (or 25 kcal/kg) for mild illness, 25 per cent of BMR (or 35 kcal/kg) for moderate illness and 50 per cent of BMR (or 45 kcal/kg) for severe illness.

Protein requirement

The human body cannot synthesise 9 of the 22 known amino acids and these must therefore be supplemented in food. These 9 amino acids which are also referred to as *essential amino acids*, are threonine, valine, leucine, isoleucine, methionine, lysine, phenylalanine, tryptophan and histidine. These essential amino acids must constitute about 20 per cent of the total protein intake. The daily loss of endogenous proteins in urine, feces, sweat and other body fluids is approximately 0.4 mg/kg. Hence if all dietary protein were to be fully utilised (that is, if the *biological value or* percentage of nitrogen-retained/nitrogen-absorbed was

very high), this amount (that is, 0.4 mg/kg) would be sufficient for daily protein replenishment. However, making allowances for a variable digestion (that is, variable *digestibility coefficient* or percentage of absorbed protein/ingested protein) and variable biological value, the recommended intake of protein for an adult is about 1g/kg.[1] Pregnancy and lactation are physiologic states requiring additional dietary proteins (additional 15–25 g/day). The growing child also requires about 1.5–1.8 g/kg protein daily during the first decade of life.

The two main sources of protein are plant sources (pulses, cereals) and animal sources (eggs, milk, meat). The plant sources of proteins (vegetable proteins) are often biologically *incomplete* (that is, lacking some essential amino acids) when considered individually. Thus cereal proteins are deficient in lysine and pulses are deficient in methionine.[2] Animal proteins are more complete biologically. The biological value of most animal proteins varies from 80–95 per cent whereas that of plant proteins ranges from 50–70 per cent.

Illness, in general, increases protein requirement. Roughly, for a mild illness the increased daily protein requirement is 0.6–0.8 g/kg, for moderate illness 0.8–1.0 g/kg and for severe illness 1–1.5 g/kg.

Carbohydrate requirement

Carbohydrates are a primary and the main source of energy for living beings. They are also required for the synthesis of some non-essential amino acids and for the oxidation of fats. The carbohydrates in a balanced diet must provide about 50–70 per cent of the total energy intake. Dietary carbohydrates include starches (present in abundance in cereals, millets, roots and tubers), sugar (glucose, sucrose, fructose, lactose) and cellulose.

Fat requirement

Apart from being concentrated sources of energy, fats are also required for the proper supply of *essential fatty acids,* such as linoleic, linolenic and arachidonic acid. These fatty acids are essential for normal growth, hemostasis, body defence and dermal integrity. The daily requirement is about 5 g/day (3 per cent of the total energy consumption), vegetable oils (with the exception of coconut oil) being very rich sources.

Regarding the total fat requirement, it has been suggested that about 20 per cent of dietary calories must come from fats. This amounts to an intake of about 10–20 g of fat per day.

Requirement of vitamins and minerals

Tables 5.1–5.3 depict the daily requirement of various vitamins and minerals alongwith features of their deficiency and excess.

PROTEIN ENERGY MALNUTRITION (PEM)

Epidemiology According to worldwide estimates, there are about 500 million people who are malnourished all over the world. About 60 per cent of them live in south Asia. Figures from India indicate a prevalence of severe malnutrition ranging from 1–3.8 per cent in preschool children and accounting for about 15 per cent of pediatric admissions in hospitals. Lesser degrees of malnutrition are found in 20–30 per cent of preschool children.

Protein energy malnutrition affects children in the under-five age group. It contributes significantly to childhood morbidity and mortality as also to the physical and mental retardation of the affected children.

[1] This assumes a net protein utilisation (NPU), equal to the product of biological value and digestibility coefficient, of 65 for an Indian diet.

[2] Perhaps this explains the traditional practice of combining a cereal with a pulse, for example, rice and sambar, or roti and dal, in an Indian diet.

Table 5.1 Water soluble vitamins

Vitamin	*Function*	*Source*	*Recommended dietary allowance*	*Deficiency*	*Assay for deficiency*	*Toxicity*
Thiamine B_1	as cofactor *thiamine pyrophosphate* (TTP) in – decarboxylation of pyruvate (Kreb's cycle); – decarboxylation of α-ketoanalogues of branch chain amino acids – as transketolase in hexose mono-phosphate pathway; – production of ribose 5 phosphate (nucleic acid synthesis); – production of NADPH for fatty acid synthesis	cereals (unmilled) pulses, nuts (esp. groundnuts) milk, meat, eggs, (vegetables are relatively poor sources)	0.5 mg/1000 kcal	*Dry beriberi*— loss of ankle/ knee jerks, sensory loss, calf muscle pain *Wet beriberi*— above + circulating congestion, peripheral edema high output state *Wernicke's encephalopathy*— ataxia, opthalmoplegia *Korsakoff psychosis*— confabulation and memory loss *Infantile beriberi*— aphonia cardiac failure	decreased erythrocyte transketolase activity	none known
Riboflavin B_2	as coenzyme *flavin adenine dinucleotide* in mitochondrial oxidative phosphorylation, Kreb's cycle, fatty acid β-oxidation	liver, meat, eggs, vegetables; pulses are relatively poor sources	0.6 mg/1000 kcal	angular stomatitis/ palpebritis, cheilosis, glossitis, corneal vascularisation, nasolabial dermatitis, scrotovulvar dermatitis	decreased erythrocyte glutathione reductase	none known
Niacin (nicotinic acid)	as coenzyme NADPH/NADH in glycolysis, fatty acid synthesis, Kreb's cycle, oxidative phosphorylation	liver, meat, pulses, cereals, milk niacin in non-absorbable form	6.6 mg/1000 kcal	*pellagra*— dermatitis, (exposed parts) dementia, diarrhea, death (4ds) cheilosis, peripheral neuropathy, myelopathy, malar pigmentation, scrotolvulvar dermatosis	decreased urinary N-methyl nicotinamide	skin flushing, headaches, tingling

Table 5.1 Water soluble vitamins (contd.)

Vitamin	*Function*	*Source*	*Recommended dietary allowance*	*Deficiency*	*Assay for deficiency*	*Toxicity*
Pyridoxine B_6	as pyridoxal phosphate in transamination desulfuration deamination of amino acids; decarboxylation reactions in synthesis of epinephrine, histamine, serotonin; synthesis of porphyrins, sphingolipids and niacin	liver, meat, cereals, legumes	1.5 mg/day	cheilosis, glossitis, stomatitis, nasolabial seborrhea, acneiform rash, peripheral neuropathy, depression, seizures, oxalate renal calculi	increased urinary xanthurenic acid	liver damage
Pantothenic acid	as part of coenzyme A in Kreb's cycle; synthesis of cholesterol, phospholipids, porphyrins; β-oxidation fatty acids	widespread animal and plant sources	1 mg	*burning feet syndrome*, leg cramps, fatigue		none known
Biotin	– activator for carboxylases – synthesis of cholesterol – gluconeogenesis	liver, meat, nuts, milk, fruits	30–100 μg	eczematoid dermatitis glossitis, paresthesias cramps, dry skin, hypercholesterolemia		none known
Folic acid	as *tetrahydrofolate* in transfer of single carbon anticonvulsants units in synthesis of nucleic acids, methionine, serine formation of heme	liver, eggs, leafy vegetables	adult: 100 μg; pregnancy: 300 μg; lactation: 150 μg	glossitis *megaloblastic anemia* impaired weight loss, diarrhea	decreased red cell folate, plasma folate	large dose antagonises

Table 5.1 Water soluble vitamins (contd.)

Vitamin	*Function*	*Source*	*Recommended dietary allowance*	*Deficiency*	*Assay for deficiency*	*Toxicity*
Cobalamine B_{12}	as *extrinsic factor* for absorbtion; synthesis of nucleic acids, purines, pyrimidines, myelin, folate synthesis	liver, meat, foods of vegetable origin are poor sources	adult: 1 μg (including pregnancy, lactation); infant: 0.2 μg; children: 0.2–1 μg	glossitis *megaloblastic anemia, subacute combined degeneration* of spinal cord, achlorhydria	decrease plasma B_{12}, Schilling test positive	none
Ascorbic acid	antioxidant, synthesis of collagen; resistance to infections; iron absorption hemostasis and wound healing; synthesis of norepinephrine and oxidation of phenylalanine to tyrosine	fruits, leafy vegetables, meat, milk are poor sources	adult: 40 mg (including pregnancy); infant: 20 mg; lactation: 80 mg	inflamed bleeding gums, perifollicular hemorrhages, follicular hyperkeratosis, stiff limbs, swollen ankles, spread legs, 'scurvy' *infants :* pseudoparalysis, purpura, epistaxis, retrobulbar hemorrhage, *'ground glass'* bones on X-ray	decreased platelet ascorbic acid	urate, cystine and oxalate renal stones, false +ve test for urine sugar, fecal occult blood

*cereals include rice, wheat, barley, oats and millets (jowar, maize, bajra, ragi, kodu) pulses include grams (dals), peas, beans

Table 5.2 Fat soluble vitamins

Vitamin	*Function*	*Source*	*Recommended dietary allowance*	*Deficiency*	*Assay for deficiency*	*Toxicity*
Vitamin A* (retinol)	combines with opsin to form rhodopsin of retina; growth and development of skeletal and soft tissues; enamel formation; maintenance of normal epithelium;	fish, milk, green vegetables, carrot, sweet potato, mango papaya	adults: 750 μg retinol; children less than 6 years 300 μg children between 6–12 years: 600 μg	conjunctival, corneal xerosis, Bitot's spots, keratomalacia, night blindness, follicular hyperkeratosis	plasma vitamin A less than 10 μg/ 100 ml	**acute :** transient hydrocephalus, vomiting **Chronic :** stunted growth, bone pain, dry scaly skin/hair loss,

* Vitamin A reduces risk of death and complications from measles, and infant mortality rate

Table 5.2 Fat soluble vitamins (contd.)

Vitamin	*Function*	*Source*	*Recommended dietary allowance*	*Deficiency*	*Assay for deficiency*	*Toxicity*
	reproduction and lactation; antineoplastic role					yellow skin (except sclera), pseudotumour cerebri, hepato-splenomegaly, fever
Vitamin D (chole-calciferol)	normal mineralisation and formation of bones, teeth; absorption of calcium from the gut	sunlight, foods of animal origin (fish, butter, eggs, milk)	adults: 2.5 μg (100 IU); pregnancy and lactation: 10 μg (400 IU); infants and children: 5 μg (200 IU)	*adults:* affects long-bones osteomalacia, fragile bones *children:* rickets, rachitic rosary, knock knees, bowed legs, muscular hypotonia, *infants:* craniotabes, skull bossing X-ray concave cupping and broadness of epiphyses, coarse trabeculae, irregular metaphyses	serum alkaline phosphatase	anorexia nausea, polyuria, vomiting, bone and soft tissue calcification, renal impairment
Vitamin E (tocopherol)	intracellular antioxidant; prevents lipid peroxidation	cereals, pulses, milk, eggs	adults: 10–30 mg/day; children: 5 mg/day	spinal cord postcolumn degeneration, ceroid pigment deposition in smooth muscle, myopathy, creatinuria, hemolysis in infants fed on cow's milk	plasma tocopherol, erythrocyte hemolysis test	interference with vitamin K and delayed clotting, headaches, abdominal pain
Vitamin K	synthesis of coagulation factors II, V, IX, X and possibly V (for posttranslation γ carboxylation)	green leafy vegetables, cereals, egg, cheese	adults: 70–140 μg; children: 15–50 μg	hemorrhage	hemolytic anemia	

Table 5.3 Trace elements and other minerals

Vitamin	*Function*	*Source*	*Recommended dietary allowance*	*Deficiency*	*Assay for deficiency*	*Toxicity*
Calcium	bone and teeth formation; muscle and nerve physiology; essential in blood coagulation	milk, cereals, fish	adults: 400–500 mg pregnancy and lactation: 100 mg children: 500–700 μg	bone demineralisation, hypocalcemic tetany, Chvostek and Trousseau signs, laryngospasm, convulsions, osteomalacia, rickets	serum calcium	constipation, abdominal pain, polyuria nocturia, metastatic calcification, renal failure, muscle weakness
Phosphorus	bone and teeth formation; component of nucleic acids, phospholipids acid base buffer systems; phosphorylation reactions in intermediary metabolism	milk, beverages, cereals, bread	adults: 1000 mg pregnancy and lactation: 1500 mg	weakness, paresthesias, bone pain	serum phosphorus	neuroexcitability, tetany, convulsions
Magnesium	component of bone, teeth; nerve and muscle physiology; activator of all kinase reactions involving ATP; potassium-calcium balances	milk, vegetables, cereals, pulses	adults: 200–300 mg	neuromuscular irritability tetany, depression of tendon reflexes, respiratory arrest, cardiac irritability refractory hypokalemia, paralysis	serum magnesium	diarrhea, hypotension, paralysis, respiratory depression
Iron	component of heme, cytochrome oxidase, catalase, myoglobin	liver, meat, egg, green leafy vegetables	adults: 25 mg pregnancy and lactation: 40 mg	microcyte hypochromic anemia, decreased work capacity, stomatitis, postcricoid stricture, dysphagia*, pica**, koilonychia, brittle nails	serum iron	hemolysis, diarrhea, hepatic failure, diabetes, testicular atrophy, cardio-myopathy, skin dis-colouration, arthritis

* called the Plummer-Vinson or Patterson-Kelly syndrome; ** eating inedible items such as mud (geophagia), ice (pagophagia)

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Table 5.3 Trace elements and other minerals (contd.)

Vitamin	*Function*	*Source*	*Recommended dietary allowance*	*Deficiency*	*Assay for deficiency*	*Toxicity*
Copper	essential for heme synthesis, iron mobilisation, mineralisation, connective tissue metabolism, melanin formation; activator of tyrosinase cytochrome oxidase, MAO, dopamine hydroxylase; essential in electron transport system	meat, cereals, cocoa, raisins	adult: 2–6 mg	hypochromic normocytic anemia, leukopenia, osteopenia, kinky hair *(Menke syndrome)*, poor growth	serum copper, plasma cerulo-plasmin	hemolytic anemia, hepatitis, Kayser Fleischer ring, bronze skin colour, metallic taste, renal dysfunction, hypersalivation
Zinc	component of insulin, metallo-enzymes transferases, hydrolases; enhances cellular immunity and protein synthesis	meat, milk	adults: 15 mg; pregnancy and lactation: 25 mg	acrodermatitis enteropathica, (diarrhea, eczematoid skin rash) delayed wound healing, decreased taste, anemia, hypogonadism	serum zinc, urine zinc	nausea, vomiting, abdominal cramps, pancreatitis, anemia, pulmonary edema
Selenium	antioxidant, component of glutathione peroxidase	cereals, eggs, onions	0.05–0.2 mg	cardiomyopathy (Keshan disease in China), cataract, myopathy	urine selenium	dental caries, anorexia, garlic odour, hair loss
Chromium	co-factor with insulin, essential for glycogenesis, lipogenesis, protein synthesis	cereals, meat	0.05–0.2 mg	insulin resistance, impaired glucose tolerance	urine chromium	dermatitis, lung cancer
Manganese	essential in oxidative phosphorylation, cholesterol synthesis	cereals, green vegetables	2–5 mg	weight loss, bleeding disorder hypocholesterolemia, dermatitis	serum manganese, urine manganese	Parkinsonism-like disease, psychosis, ataxia
Iodine	constituent of thyroid hormones	seafoods, spinach, meat, vegetables	men: 0.14 mg; women: 0.10 mg	goitre, mental deficiency	thyroid function tests	nervousness, tremors, sweating

Table 5.3 Trace elements and other minerals (contd.

Vitamin	*Function*	*Source*	*Recommended dietary allowance*	*Deficiency*	*Assay for deficiency*	*Toxicity*
Molybdenum	Xanthine metabolism	meats, cereals	0.2–0.5 mg	headaches, lethargy, esophageal cancer, abnormal metabolism of sulphur containing amino acids	urine molybdenum	gout-like syndrome
Cobalt	methionine metabolism interacts with iodine		0.0001 mg	anemia (see vitamin B_{12} deficiency)		goitre, cardiomyopathy

Classification (Table 5.4) Severe protein energy malnutrition can arise due to an inadequate intake of both protein and energy, or due to an inadequate intake of mainly protein. In a combined deficiency state (combined PEM or *marasmus*) there is a greater diminution in somatic protein out of proportion to the reduction in visceral proteins. The result is a chronic, moderate catabolic state, with marked loss of subcutaneous fat and muscle mass ('skin and bones' appearance) with a preservation of albumin synthesis, normal levels of transferrin and a normal lymphocyte count. When an inadequate intake of protein is the dominant factor, the subcutaneous fat and somatic proteins are spared and the visceral proteins get depleted. Serum albumin levels fall and there may be associated lymphopenia and anergy. The resultant *hypoproteinemic malnutrition* is called *kwashiorkor.*[1] In children, this is common during the second and third year of life when they are weaned from the breast. In adults, the term is used for an acute catabolic state precipitated by an event such as trauma or sepsis. It is therefore seen commonly in hospitalised patients.

[1] Kwashiorkor means the 'red haired boy' in the Ga language of Ghana in Africa. It also means the 'disease which a child gets on being displaced from the mother's breast by another baby'.

Table 5.4 Classification of malnutrition

Type of malnutrition	*Deficiency*	*Clinical features*	*Laboratory findings*
Marasmus	calories	weight less than 80 per cent predicted, triceps skin 3 mm, mid-arm circumference less than 15 cm	creatinine-height index less than 60 per cent of standard
Kwashiorkor	proteins	edema, skin changes, sparse pluckable hair*, delayed wound healing	serum albumin less than 2.8 g/dl, transferrin less than 150 mg/dl, anergy
Marasmic kwashiorkor	calories and proteins	combination of the above	combination of the above

* (Hair pluckability is tested by pulling a lock of hair from the top of the head not the sides or the back. Abnormal hair pluckability is indicated if three or more strands of hair are removed easily.)

A third state called *marasmic kwashiorkor* is seen when there is a sudden increase in the demand for protein with a background of chronic inadequate caloric and protein intake. This upsets the adaptive mechanisms in starvation which are meant to spare lean body mass. The visceral proteins themselves get depleted and the previously depleted somatic proteins cannot meet the increased body requirement for protein. The result is rapid clinical deterioration unless nutritional support is provided.

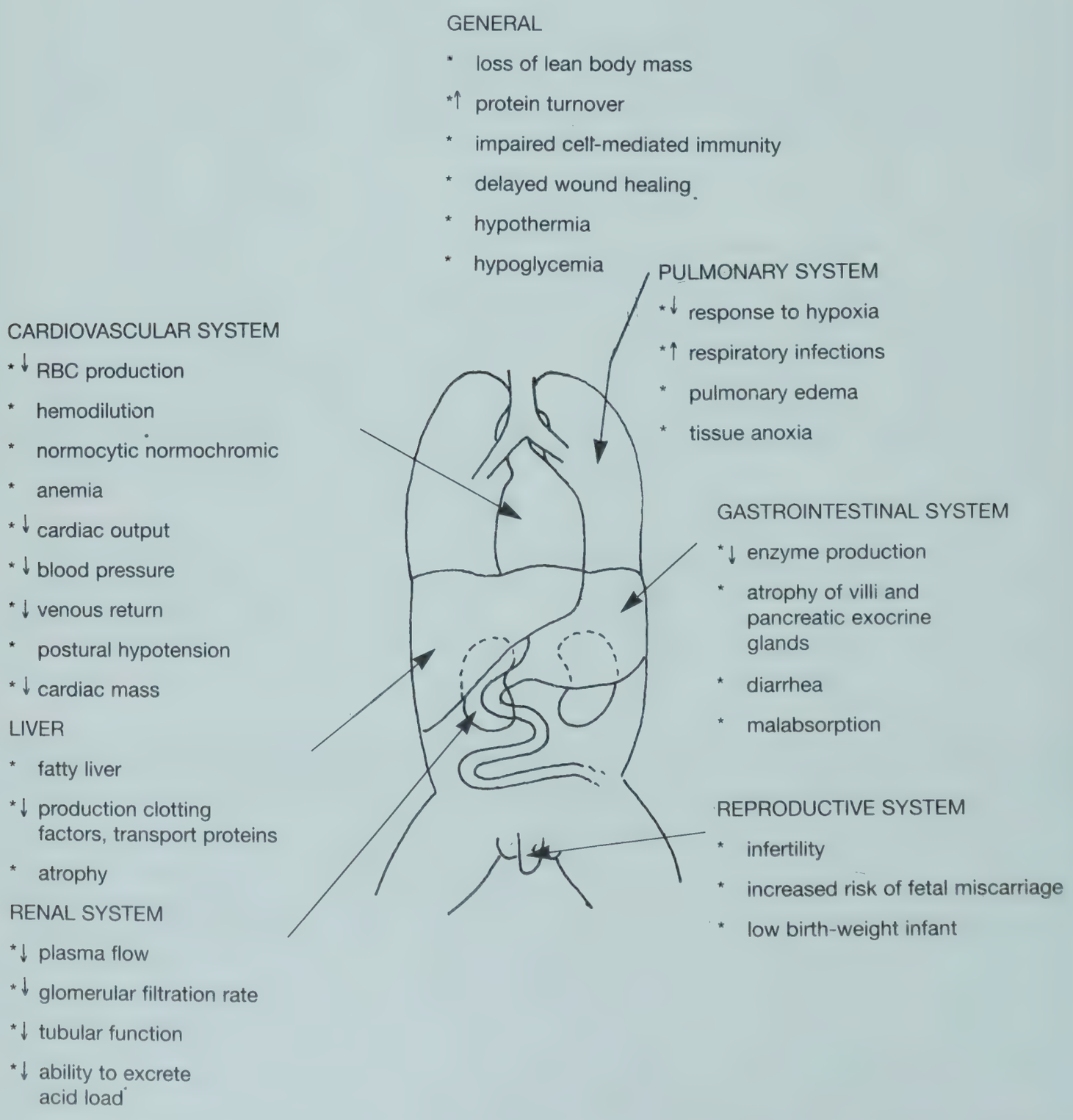


Fig. 5.3 Pathophysiologic changes in various body systems as a result of malnutrition

Pathophysiology The changes in various organ systems with protein energy malnutrition are depicted in Fig 5.3.

EATING DISORDERS

Obesity

Obesity is defined as a body weight 20 per cent or more in excess of the standardised 'ideal' body weight. Alternatively, a body mass index in excess of the 85th percentile is said to constitute obesity.

Epidemiology Socioeconomic status, age and sex are some of the epidemiologic variables that determine the prevalence of obesity. In developing countries like India, obesity is a problem of the upper socioeconomic classes. (In the developed countries, the converse is true.) Obesity also increases with age, from the fourth decade onwards and there is a slight female preponderance. Epidemiologic studies have shown that obesity increases the risk for diabetes mellitus, hypertension, atherosclerosis and premature death.

Etiology Normally, satiety and appetite are regulated by the ventral hypothalamus. The satiety centre in the ventromedial hypothalamus and the feeding centre in the ventrolateral hypothalamus interact to influence and determine the eating behaviour of an individual. This is modulated by the cerebral cortex and other psychosocial and genetic influences. Although the exact defect in obese patients has not been delineated, overeating seems to be the dominant cause. The energy intake-expenditure equation is also modified by a decreased thermic response to food in obese individuals.

Secondary causes of obesity include neurologic lesions of the hypothalamus (tumours like craniopharyngioma, trauma or inflammatory disease), endocrine causes (hypothyroidism, Cushing syndrome, rarely insulinomas) and inherited genetic disorders (*Laurence-Moon-Biedl syndrome*[1], *Prader-Willi syndrome* [2]).

Pathophysiology Obesity has been classified as due to either a childhood-acquired increase in the number of fat cells (*adipocyte hyperplasia*) or due to an adult onset increase in the size of the existing adipocytes (*hypertrophy*). Either mechanism is associated with an increase in subcutaneous fat, increase in the size of the liver, kidneys, heart and the muscles due to fat deposition. Obesity also provokes several metabolic and hormonal changes that are reversible with loss of body weight. These include hyperinsulinemia, hypercortisolism and a diminished release of growth hormone in response to stimuli. Hyperinsulinemia in these cases is the result of a diminution in the number of insulin receptors as well as due to a 'post-receptor' defect.

The inconsistencies in epidemiologic studies linking obesity to vascular death has been sought to be explained by differentiating between a '*male* or *android* or *abdominal*' type of obesity where fat is deposited in the hip region and a '*female* or *gynecoid*' type of obesity where fat is deposited in the gluteal region. Abdominal fat is metabolically more 'active' and hence abdominal obesity (defined by an increase in the ratio of waist/hip circumference of more than 1 in men and more than 0.8 in women) linked to vascular disease.

The consequence of *mild–moderate* obesity (exceeding ideal body weight by 15–30 per cent and 30–50 per cent, respectively) include an increased incidence of hypertension, hyperlipemia, diabetes mellitus, premature coronary atherosclerosis, cholelithiasis, varicose veins, venous thrombosis, osteoarthritis and endometrial carcinoma. *Morbid obesity* (defined as exceeding ideal body weight by 100 per cent or

[1] The Lawrence-Moon-Biedl syndrome is characterised by retinitis pigmentosa, polydactyly and mental retardation besides obesity.

[2] The Prader-Willi syndrome is associated with hypotonia, mental retardation and is linked to chromosome 15.

more) is associated with sudden death, obesity hypoventilation syndrome (Pickwickian syndrome), congestive heart failure and nephrotic syndrome.

Treatment The therapeutic modalities used for treating obesity include aerobic exercise, a low-calorie diet, behavioural therapy, pharmacologic therapy and surgery.

Of these, aerobic exercise and a significantly low-calorie diet (300–600 kcal/day) have been tried widely with good results. *Behavioural therapy* includes self-monitoring, control of stimuli that precede eating and development of techniques to control the act of eating along with reinforcement of the prescribed behavior. *Pharmacologic therapy* has not been proven to be very effective and has a potential for causing undesirable side effects. Anorectic drugs used include fenfluramine and diethylpropion. Newer appetite suppressants tried include fluoxetine and femozitene (antidepressants which are serotonin uptake inhibitors). Parenteral analogues of cholecystokinin have been tried with the view to causing early satiety and threochlorocitric acid has been used to delay gastric emptying. Inhibitors of carbohydrate absorption (acarbose) and lipid absorption (sucrose, polyester, tetrahydrolipostatin) have been used but are limited by gastrointestinal side effects and steatorrhea. Perhaps *thermogenesis enhancers* (new β-agonists), currently being tried, may yield better results.

Surgical procedures are palliative and are used only for morbid obesity. They include bypass procedure of the stomach (*gastric bypass*) or small intestine (*jejuno-ileal bypass*) that limit absorption, and gastric stapling (a gastric pouch of a smaller size is created that limits the amount that can be eaten).

Prevention Preventive measures include fostering healthy dietary practices from childhood onwards and health education stressing the harmful effects of overeating. Food should be consumed principally for nutrition and only to a limited extent for pleasure.

Anorexia Nervosa

Anorexia nervosa is a disorder, mostly of teenage girls, characterised by *self-inflicted weight loss* (due to anorexia), a *secondary endocrine problem* (amenorrhea or loss of libido) and a *psychologic disorder* manifested by a morbid fear of eating.

Etiopathogenesis This disorder is probably the result of a complex interaction of a genetic-cum-physiologic predisposition with a psychologic predisposition fostered by the social milieu of the individual (usually a woman). The typical patient is an otherwise well-adjusted, intelligent person who, under the influence of endocrinal stresses, becomes relentlessly preoccupied with diet and a *'thin body' image* leading to an all-pervading obsession that replaces all other personal and social pursuits. There is also an increased incidence of depression in the families of these patients, which may be contributory.

Pathophysiology and clinical features Reduced intake of food leads to a fall in plasma glucose and serum insulin levels with a shift to a *fat mobilising* metabolism (increased lipolysis along with glycogenolysis and ketogenesis. There is diminished peripheral conversion of T_4 to T_3 (resulting in bradycardia, hypercarotenemia, coarse hair and constipation) and a diminution in serum catecholamines. The hypothalamus shows an 'adaptive' reduction in release hormones and this results in reduced levels of pituitary gonadotropins (accounting for the amenorrhea, infertility and loss of libido). Weight loss exceeds 25 per cent of previous weight. Many patients have associated *bulimia*, that is, they go through periods of massive eating ('binge eating') followed by self-induced vomiting or laxative abuse (to get rid of the consumed food).

Treatment Mild forms of the illness are tackled by educative discussions with the patient and her family and a supervised incremental diet. Severe forms may require hospitalisation to correct dehydration, electrolyte imbalances and under-nutrition. This must be coupled with psychotherapy.

DIETARY FIBRE IN HEALTH AND DISEASE

Dietary fibre is a general term used for a widely diverse group of complex (non-starch) carbohydrates of differing chemical structures and physical properties which are not digestible by human intestinal enzymes.

Types Broadly speaking, there are two categories of dietary fibre: 1) the *fibrous* or *insoluble* (particulate) compounds, for example, cellulose, lignin (bran); 2) the *viscous* or *soluble* (gel-forming) non-cellulose carbohydrates—pectins, gums, mucilage, hemicellulose.

Effects Fibrous carbohydrates have their greatest effect on the colon whereas the viscous fibres modulate the small intestinal function. Both types can undergo colonic fermentation producing short chain fatty acids. Viscous fibre reduces postprandial increases in glucose and plasma insulin levels, possibly secondary to a reduced rate of gastric emptying. It may also lower cholesterol by altering the enterohepatic recirculation of bile salts and lipoproteins. Particulate fibre increases stool bulk, holds water, reduces intracolonic pressure and decreases large bowel transit time.

Role in disease A decrease in dietary fibre has been shown to be associated with an increased prevalence of constipation, diverticulosis, diabetes mellitus, colonic cancer and obesity in epidemiologic studies.

A high fibre diet has been used in the therapy of chronic constipation, diverticulosis, irritable bowel syndrome and diabetes mellitus.

DISEASES DUE TO NUTRITIONAL TOXINS

Fluorosis

Fluorosis is a disorder arising from the excessive ingestion of fluorides.

Pathophysiology Fluorides normally protect against dental caries. They are required for the formation and maintenance of healthy teeth and bones. They are *carioprotective* because the fluoride ion inhibits bacterial metabolism in the caries plaque and promotes remineralisation of the enamel in the early carious lesion. This protection is maintained only if the water which washes over the teeth has a fluoride content of 1 ppm[1] (a level of 0.6–0.7 ppm would seem optimal in hotter climates with high water consumption). Fluorides also confer indirect benefits on the teeth since a decrease in incidence of caries avoids premature extraction of teeth which in turn decreases the incidence of malocclusion. The tissue in the body most sensitive to excessive ingestion of fluoride is the ameloblastic layer of the teeth (which forms the organic framework of the enamel). Excess fluoride causes dental hypoplasia with areas of hypocalcification and hypo-mineralisation in the enamel, which thus appears mottled. This is called *dental fluorosis*. It occurs when ameloblasts are affected; as a result maturation of the enamel is delayed and the general mineralisation processes inhibited. Dental fluorosis, therefore, does not occur once the development of teeth is complete.

The excess of fluoride also accumulates in the bone, trabecular bone uptake being more than that of the compact bone. It is incorporated as *fluorohydroxyapatite crystals*. The result is a disordered lamellar orientation of the compact bone, a poorly-formed Haversian system and an increase in poorly mineralised osteoid (mimicking osteomalacia). The fluoro-

[1] ppm : parts per million.

hydroxyapatite crystals also stimulate osteoblasts, possibly by increasing the flow of piezo-electric current in the bone. This results in hyperostosis. The bones are heavy and the new bone formation extends to the ligaments, joint capsules and interosseous membranes. Osteophytes become abundant, intervertebral ligaments ossify and the spinal canal is narrowed. The whole spectrum of skeletal changes is referred to as *skeletal fluorosis.*

Epidemiology Dental fluorosis predominantly affects the permanent teeth of children whereas skeletal fluorosis is a disease found in adults. An increased fluoride content of drinking water or an increased occupational exposure (aluminium production, magnesium foundries, fluorosis processing, super phosphate manufacture) may be responsible. In certain states of India (notably Andhra Pradesh, Tamil Nadu, Karnataka, Kerala, Rajasthan and Punjab) the disorder is widespread. A variant of skeletal fluorosis presenting in childhood as *genu valgum* has been, reported from some districts of Andhra Pradesh where the intake of *jowar* (a millet with affinity for fluoride) is high.

Clinical features Dental fluorosis manifests as a mottled enamel of the permanent teeth (especially the upper incisors) in children. The deciduous teeth may also show changes. A grading system has been proposed: *grade 1* or early dental fluorosis manifests as white opacities and faint yellow lines across the enamel. In *grade 2* dental fluorosis, the teeth acquire a distinct brown stain and in *grade 3* or advanced dental fluorosis, the teeth have a pitted appearance with chipping of the edges. In very severe fluorosis the incidence of caries may increase due to exposure of dentine consequent to a loss of the enamel, and secondary stains from the oral cavity may further discolour the mottled areas. In adults, severe localised destruction of the jaw bones has been described.

Skeletal fluorosis is seen in adults, especially males. Poor dietary intake of protein and calcium and hard manual labour predispose to severe skeletal changes. The patients complain of polyarthralgias, stiffness of back, diminished mobility and may acquire flexion deformities and a thoracic kyphosis. Neurologic symptoms are frequently seen especially in parts of Punjab. The bony overgrowths (exostoses) within the spinal canal and vertebral osteophytes impinge on the spinal cord and the nerve roots respectively. Thus the typical presentation is of an insidious onset *radiculomyelopathy.*[1] Since the skeletal changes are most prominent in the upper thoracic-cervical vertebral column, there is typical involvement of all four limbs. Paresthesias, sensory changes and root pains with asymmetrical muscle wasting are common findings in the upper limbs, while the lower limbs are commonly involved in a spastic paraparesis. Posterior column (dorsal cord) involvement is a prominent feature and occasionally quadriparesis is seen. The disorder tends to be rapidly progressive. One important clinical clue to the diagnosis (apart from residence in an endemic area and the pattern of neurologic involvement) is the palpation of bony overgrowths (exostoses), especially prominent over the medial border of the tibia. Vascular calcification (common iliac, femoral, radial arteries) has also been reported in some patients. In children skeletal fluorosis is seen (in certain parts of India and also in South Africa, Tanzania) presenting as *genu valgum* and *sabre shins.*

Investigations A skeletal survey for evidence of skeletal fluorosis is indicated when there is a high index of suspicion of the disorder. The radiological changes are also graded into three categories. *Grade 1* fluorotic changes are characterised by the roughening and blurring of the trabeculae of the pelvis and spinal column. In *grade 2* fluorotic changes, the trabecula

1 Combination of nerve root (radiculo) and spinal cord (myelo) compression

merge and the bone has a diffuse structureless appearance with an uneven contour, narrowed medullary cavities and calcification of the ligaments. These changes are most marked in the pelvis, spine and ribs. *Grade 3* skeletal fluorosis is characterised by bony exostoses, calcification of the interosseous membranes and marble bones. These radiologic changes mimic those in ankylosing spondylitis, ochronosis and diffuse idiopathic skeletal hyperostosis, which is a rare disorder.

Blood and urine levels of fluoride can be estimated (if facilities are available). In patients with fluorosis, the blood fluoride level averages 1.5 ppm and the urine fluoride level is about 8.0 ppm.

Treatment There is no effective treatment for established fluorosis. Some improvements have been reported with enteric coated preparation of serpentine (magnesium metatrisilicate) in a dosage of 50 mg twice a day. Surgery for compressive myelopathy has several problems; the bone is 'hard' to handle surgically, and severe hypocalcemia (manifesting as intraoperative hypotension) may result due to the release of fluoride from the bone.

Prevention The best way to counter fluorosis is to prevent it by *defluoridation* of drinking water. The methods used are as follows:

1. for soft water, an *ion exchange process* using granules of tricalcium phosphate;
2. activated alumina/bone char for *fluoride trapping*;
3. *domestic defluoridation,* using sulphonated sawdust;
4. for hard water, the *lime soda process* of softening can be used. Fluoride is removed along with the magnesium.

Venoocclusive Disease or Endemic Ascites

This disorder due to the ingestion of *pyrrolizidine* alkaloids is discussed in detail in the section on portal hypertension.

Epidemic Dropsy

Epidemic dropsy is a disorder characterised by outbreaks of epidemics of dropsy[1] or 'a generalised edematous state'.

Epidemiology Epidemic dropsy occurs due to contamination of edible oil (usually mustard oil) with seeds of the 'prickly poppy' (*Argemone mexicana*). Prickly poppy grows wild in India and its seeds resemble mustard seeds. Further, mustard is harvested in March, the time the seeds of 'prickly poppy' also mature. So, chance contamination of mustard seeds with prickly poppy seeds is possible. A deliberate adulteration of mustard oil by unscrupulous traders is also encountered. The peak incidence of epidemic dropsy is in July-August, reflecting the interval between the harvesting of mustard and the extraction and marketing of mustard oil. Adults and children of both sexes are affected; only the very young and breastfed infants (who are not fed regular food) are spared. The disorder has been reported from pockets of east and central India, that is, the states of West Bengal, Orissa, Bihar, Uttar Pradesh and Madhya Pradesh.

Etiopathogenesis The seeds of the prickly poppy contain the alkaloid *sanguinarine* which is a potent metabolic toxin which inhibits pyruvate metabolism. The accumulation of pyruvate is associated with a generalised vasodilatation with an increased arteriolar and capillary permeability, a situation akin to wet beriberi. The result is a non-inflammatory extracellular water sequestration, affecting the skin and subcutaneous tissue, mucous membranes, uvea, heart and serous cavities. This manifests as edema, pleuropericardial and peritoneal effusions, glaucoma, a high output circulatory congestive state and dermal telangiectasia.

Clinical features The disease is usually insidious in onset, with gastrointestinal symptoms of abdominal pain and a watery

[1] Dropsy means generalised fluid accumulation.

diarrhea being prominent initially. Soon a pitting peripheral edema appears, which may progress to a generalised anasarca, depending on the severity of the disease. In severe cases, a state of circulatory congestion (like wet beriberi) may develop. Cutaneous manifestations include prominent telangiectasia and nodular hemangiomata, the latter reflecting dermal neovascular proliferation. Involvement of the uveal tract can cause glaucoma. Altered permeability of pulmonary capillaries can lead to pulmonary edema. There is, however, no evidence of any peripheral neuropathy, enabling a differentiation from wet beriberi.

Natural history and treatment In severe cases, the mortality may be as high as 50 per cent, with cardiovascular decompensation being the leading cause of death. Treatment is mainly supportive, with diuretics, salt restriction and rest.

Prevention A simple *ferric chloride test* (the latter forms an orange red precipitate with sanguinarine) helps to detect contaminated mustard oil. Strict testing of mustard oil before marketing, enforcement of the 'Prevention of Food Adulteration Act' and the education of farmers (who harvest the crop) are some measures that will help prevent epidemic dropsy.

Neurolathyrism

Human lathyrism or neurolathyrism is a neurotoxic disease caused by the ingestion of certain lathyrus species (*L. sativus, L. cicera*) and characterised by clinical signs of irreversible pyramidal tract dysfunction.

Epidemiology Lathyrism is found in many states of India such as Jammu and Kashmir, Punjab, Bihar, Rajasthan and West Bengal. Central India has a particularly high prevalence rate. A survey carried out between 1956 and 1961 revealed 25,000 cases in Rewa district and 7,000 cases in the Satna district of Madhya Pradesh. Men are affected more than women and the age group 10–40 years is the most afflicted. The disease appears when *Lathyrus sativus* (also called *kesari dal*) constitutes more than two-thirds of the diet for a period of at least 3–6 months. Epidemics occur under conditions of famine when other food crops are damaged or destroyed. *L. sativus* being hardy, then survives and becomes the survival food. The disorder is also seen in areas where workers are paid grain as wages; one such mixture of Bengal gram, wheat and *L. sativus* (called *birri*) has a lathyrus content of 60 per cent. *L. sativus* is also used to adulterate Bengal gram and consumption of the adulterated *dal* predisposes to lathyrism.

Pathophysiology The toxic principle in *L. sativus* seed is a free non-protein amino acid B-N oxalylamino L-alanine (BOAA). BOAA is an excito-toxic glutamate analogue that interferes with the uptake of glutamate at neuronal synapses.[1] Neuropathology reveals degeneration of cortical Betz cells and of the anterior and lateral corticospinal tracts throughout the spinal cord.

Clinical features The onset of disease is usually sudden, and manifestations of central nervous system overactivity dominate the clinical picture initially. The earliest signs are nocturnal calf muscle spasms, known locally as '*lodakas*', that are extremely painful and last about 15–20 minutes. Along with muscle cramps, there may be tremulousness or coarse involuntary movements of the upper limb and a subjective 'feeling' of motor weakness in the legs. About 50 per cent of patients have this 'mild' form of disease that ceases to progress if lathyrus intake is stopped. In the rest, walking disability appears, taking the form of a spastic paraparesis. The vast majority of affected individuals walk

[1] A related toxin BMAA (β-methyl amino alanine) present in cycad nuts, consumed by the Pacific islanders, causes a type of motor neuron disease.

abnormally (stiff-legged gait with an adductor spasm) but without any aid (*no stick stage*). Others develop gastrocnemius spasm and walk on their soles in a scissoring gait with the help of a stick (*one stick stage*). With further disease severity, two sticks are required for walking (*two stick stage*), culminating finally in the *crawler stage* wherein due to gastrocnemius and adductor contractures, the patients crawl on their knees. Classically, there is a pure motor spastic paraparesis with no bladder involvement or sensory loss. The upper limbs are spared but may show subtle signs of involvement in the form of brisk tendon reflexes. The lower limb muscle tone is increased, along with brisk knee jerks, ankle clonus and extensor plantar reflexes, indicative of corticospinal tract involvement. Rarely, a sensory peripheral neuropathy attributed to segmental demyelination may coexist.

Treatment In early disease, stopping the consumption of *Lathyrus sativus* can lead to a reversal of mild symptoms. There is no treatment for the late irreversible stages of the disease.

Prevention Attempts to ban the cultivation of kesari dal have been unsuccessful. Food processing techniques, notably *parboiling*, have been used to leach out the toxin. In parboiling, the seeds are initially soaked in lukewarm water and later exposed to steam for 15 minutes. Crops that are as hardy as lathyrus (like barley) can also be promoted under conditions of water shortage.

Aflatoxicosis

Aflatoxicosis is an illness arising out of the consumption of food contaminated with toxins produced by certain strains of *Aspergillus flavus* and *A. parasiticus.*

Etiology Aflatoxins are 'bisfurano' coumarin compounds. There are four naturally occurring types – B_1, B_2, G_1, G_2[1] of which B_1 and G_1 are the commonest and most toxic. They are produced by the fungus species mentioned above, under favourable conditions of humidity (about 16 per cent) and temperature (10–37°C). They are metabolised by the hepatic microsomal enzyme systems to 'aflatoxicols'. These aflatoxins form epoxides that bind to DNA, inducing mutations (and thereby serving as proximal carcinogens), bind to DNA dependent RNA polymerase (inhibiting protein synthesis), interfere with mitochondrial electron transport systems and cause activation and leaking of lysosomal enzymes.

Epidemiology Chronic prolonged ingestion of aflatoxins (related to groundnut contamination or consumption of stored groundnut paste) has been linked to an increase in hepatocellular carcinoma in certain areas of the world — Kenya, Swaziland, Mozambique and Thailand.

Acute toxic hepatitis has been reported from India, over two hundred cases being reported in an outbreak in three adjoining districts of Rajasthan and Gujarat during the last few months of 1974. It was found that, following unseasonal rains, the maize crop had been harvested prematurely and the cobs (along with the coverings) stored in baskets. The combined heat and humidity promoted the growth of the fungus in maize. The outbreak, which started with consumption of rotting maize, lasted until the stock was consumed.

Pathology The histologic features of acute aflatoxicosis include severe ballooning of hepatocytes, profuse proliferation of biliary ductules, centrilobular scarring with edema and collagenisation of the central veins.

Clinical features In the Indian outbreak of acute aflatoxicosis, men were affected twice as frequently as women, and infants were spared. The disease had a subacute onset with fever in

[1] B and G refer to their blue and green colours on UV fluorescence.

the majority of patients and vomiting in half of them. Rapidly developing jaundice was universal and signs of portal hypertension were present in three-fourths of the patients (ascites in 75 per cent, splenomegaly in 33 per cent). A soft hepatomegaly was seen in most patients. The clinical features suggested a subacute hepatic failure but bleeding tendency and encephalopathy were rare.

Laboratory features There was leucocytosis in the peripheral blood with a predominantly conjugated hyperbilirubinemia and elevated transaminases.

Clinical course In the Indian outbreak, the overall mortality was 10 per cent, most patients having recovered over a period of a few weeks.

ENTERAL AND PARENTERAL NUTRITION

Enteral Nutrition

Enteral nutrition refers to the feeding of nutrients through a tube into the upper gastrointestinal tract.

Indications The enteral route, by virtue of its simplicity, safety and economy is the preferred route of nutritional support wherever access to a functional gastrointestinal tract is feasible. The presence of intestinal obstruction, intestinal fistulae and gastrointestinal bleeding constitute contraindications to enteral feeding. A general rule of thumb for the necessity of nutritional support is *seven days* or *seven per cent weight loss,* that is, nutritional support to be strongly considered if a patient has not been able to eat for seven days or if serial weight measurements show seven per cent decrease in weight from the baseline weight on admission.

Delivery methods A well-lubricated silicone or polyurethane tube can be inserted into the nostril and threaded down into the stomach (*nasogastric tube*). The length of the tube required is approximately the sum of the distance from the nose to the earlobe and that from the earlobe to the xiphoid process. The most serious complication is aspiration pneumonia which can be avoided by keeping the head end of the bed elevated to 30° for an hour after the last feed and discontinuing tube feeding if the pre-meal tube aspirate exceeds 100 ml indicating delayed gastric emptying. Passing the tube into the duodenum, occasionally aided by metoclopramide, decreases the risk of aspiration (*nasoduodenal tube*). The tube has to be replaced once in ten days. Large bore tubes predispose to mucosal erosion, gastroesophageal reflux and patient discomfort whereas fine bore tubes are likely to get blocked or yield a poor flow with viscous feeding materials, apart from a propensity to get dislodged. Hence when tube feeding is likely for six weeks or more, the use of a *gastrostomy tube* is preferable. A gastrostomy tube can be placed surgically under local anesthesia or with the help of an endoscope (*percutaneous endoscopic gastrostomy*). A gastrostomy tube can give rise to complications which can be *mechanical* (outlet obstruction, displacement, leakage aspiration), *metabolic* (fluid electrolyte imbalances, hyperglycemia) or *gastrointestinal* (nausea, diarrhea, steatorrhea). A *jejunostomy tube* has been suggested as an alternative in a patient at high risk for aspiration because duodenogastric reflux is less likely with a tube located beyond the ligament of Treitz but jejunostomy feedings require special formulation.

Feeding methods Tube feeding can be administered either as boluses *intermittently* or as a *continuous* infusion. Small intestinal tubes (nasoduodenal or jejunostomy tubes) necessitate a continuous infusion as a rapid distension of the small intestine is not well tolerated. Whether nasogastric/gastrostomy feeding should be continuous or intermittent is controversial. Bolus therapy is more convenient but has a higher incidence of diarrhea. Continuous feeding has a lesser incidence of

diarrhea but a greater risk of aspiration unless the patient is kept propped up continuously, which is likely to cause inconvenience.

Enteral formulations Commercially prepared *enteral diets* contain predefined amounts of carbohydrates, fats and proteins (the latter are di/tripeptides). *Elemental formulae* are also available and contain crystalline amino acids, medium chain triglycerides and oligosaccharides which do not require digestion and are recommended for patients with digestive abnormalities. They are, however, hypertonic and may cause diarrhea, hyperglycemia and a hyperosmolar state. Formulations specific for renal and hepatic failure are available and contain very little potassium and sodium (500 mg). *Renal formulae* contain only essential amino acids (non-essential amino acids being produced by in vivo nitrogen recycling) and *hepatic formulae* have a large quantity of branched chain amino acids (and fewer aromatic amino acids with a view to correcting the abnormal amino acid profile seen in these patients). However, neither has been shown to be clearly superior to conventional formulae. Patients with chronic obstructive airway disease have specially designed formulae with a higher contribution of fats to total calories (on the presumption that a low carbohydrate diet results in lower carbon dioxide production due to a lower respiratory quotient, and a lower arterial pCO_2 may increase exercise capacity).

Parenteral Nutrition

Parenteral nutrition (also called *hyperalimentation*) is defined as the administration of nutrients directly into the venous system.

Types and indications Peripheral parenteral nutrition utilises a peripheral vein for infusion of nutrients and central parenteral nutrition, also called *total parenteral nutrition (TPN)* requires a catheter in a central vein (usually the subclavian or the internal jugular vein) for nutrient infusion. Peripheral hyperalimentation is used wherever the use of a central line is precluded, where short-term nutritional therapy (less than five days) is required with an anticipation of a return to enteral feeding subsequently. Longer periods of peripheral hyperalimentation are associated with thrombophlebitis (if the osmolarity of the nutrient solution exceeds 600 mosm/l). Central hyperalimentation is indicated wherever enteral intake is *impossible* (as in the case of peritonitis, short bowel syndrome, acute pancreatitis or ileus), *inadvisable* (as in the case of intestinal obstruction, gut fistulae, acute exacerbation of ulcerative colitis or intractable diarrhea), *hazardous* (in comatose conditions with a risk of aspiration) or *improbable* (in chronic severe starvation). It is also occasionally indicated in hypercatabolic states such as sepsis, burns or extensive trauma. It must be remembered, however, that a functioning gastrointestinal tract is an absolute contraindication to TPN and indicates the need for enteral nutrition if nutritional support is considered necessary.

Principles In TPN, a hypertonic solution of nutrients is infused at a constant rate to avoid fluctuation of blood levels (due to the renal excretion of nutrients). Nutrients are provided in a concentrated form so that the daily fluid requirement is not exceeded. Protein infusion is used only as a means of synthesising new body protein and replenishing used protein, and not as a source of calories. Fats and carbohydrates are used as sole energy sources (usually in a ratio of 30:70). Carbohydrates are supplied as 50 per cent or 70 per cent dextrose, fat as 20 per cent intralipid solution and proteins as a 3–10 per cent amino acid solution. Major minerals ($Na/K/Cl/Ca/Mg/PO_4$), vitamins (as a combination MV)[1] and trace elements (Zn/Cu/Fe/I/Mn/Se/Cr) are also provided, the latter usually only for patients on very long courses of TPN.

[1] Vitamin K is not present in this combination and must be administered 10 mg i.m. once a week during TPN.

Monitoring and complications The patient on central hyperalimentation should have serum electrolytes and blood urea checked once daily, blood sugar and urine sugar checked four times daily and serum calcium, magnesium, phosphorus, bilirubin and liver enzymes checked once a week. Persistent hyperglycemia may reflect carbohydrate intolerance whereas an elevated blood urea may reflect protein intolerance. Fat intolerance is reflected by elevated serum triglyceride and often improves by adding heparin (1 u/ml of fat emulsion) which stimulates lipoprotein lipase, thereby improving triglyceride clearance. Other *metabolic complications* of TPN include a normal anion gap metabolic acidosis (due to an excess infusion of chloride that is corrected by substituting acetate for chloride), hypoglycemia, dyselectrolytemia, hypercapnia and trace element deficiencies. The patient on total parenteral nutrition is also at risk of venous catheter-related infections. *Mechanical complications* that may arise during insertion of a central venous catheter include pneumothorax, hemothorax, subclavian artery puncture and damage to the brachial plexus or thoracic duct. Catheter placement is, therefore, confirmed with a chest X-ray before beginning TPN infusion. To diminish the risk of venous thrombosis, the addition of 3,000 units heparin to a litre of TPN fluid has been recommended.

KEY CONCEPTS

- *BMR* is a measure of the amount of energy expended at rest; it varies with age, sex, height and weight
- Besides BMR, the body needs additional calories based on the type of work: 400–800 (sedentary), 800–1200 (light), 1200–1800 (moderate), 1800-4000 (heavy)
- Daily protein requirements to meet obligatory nitrogen losses=1.0 g/kg.
- *PEM* is a major global problem. PEM is characterised by weight loss, loss of subcutaneous fat, stunted growth, hair loss, dermatitis. Kwashiorkor refers to a state of deficiency of calories and protein; edema is prominent. GI, immune, and endocrine functions are affected in PEM. Treatment consists of protein and caloric repletion.
- *Obesity* (>20% excess of ideal body weight) has adverse consequences: hypertension, diabetes, hyperlipidemia, atherosclerosis, insulin resistance. Treatment consists of dieting, exercise, behaviour modification, and rarely, procedures like jejuno-ileal bypass.
- *Anorexia nervosa* (aversion to food) and *bulimia* (binge eating followed by vomiting) are eating disorders that affect teenagers usually women, with a fear of growing fat.
- *Consequences of vitamin deficiency*: thiamine: beriberi (dry, with neuropathy; wet, with edema); riboflavin: angular stomatitis, seborrheic dermatitis; niacin: pellagra (diarrhea, dementia, dermatitis, death); folate: megaloblastic anemia; B_{12}: megaloblastic anemia, subacute combined degeneration of spinal cord; C: scurvy; A: night blindness; D: rickets (children) and osteomalacia (adults)
- *Consequences of Vitamin excess*: A: carotenemia, increased intracranial pressure; niacin: flushing
- *Trace element deficiency*: Fe, Cu, Co: anemia; Se: cardiomyopathy; Zn: acrodermatitis enteropathica, reduced growth, immune dysfunction; F: dental caries
- *Nutritional toxins:*
  - F: fluorosis (dental, mottling; skeletal, calcification of interosseous membrane, bone enlargement with entrapment neuropathy)
  - Epidemic dropsy: due to sanguinarine in prickly poppy that contaminates mustard seeds; clinical presentation is with anasarca; positive ferric chloride test.
  - Neurolathyrism: β-oxalyl aminoalanine, an excitatory glutamic acid analogue in kesari dal causes illness; progressive spastic paraparesis
  - Aflatoxicosis: stored groundnuts harbor fungal products (aflatoxins) that can cause acute and chronic hepatic damage
- *Enteral* (via gut) and *parenteral* (blood stream infusion) nutrition are used when oral intake is not possible for prolonged periods; indications include perioperative period cancer cachexia, critical illness, inflammatory bowel disease.

6

Fluid and Electrolyte Disturbance

WATER AND SODIUM BALANCE

Water constitutes approximately 60 per cent of the body weight, the rest being formed by solids. Of the total body water, two-thirds is located within the cells and a third is extracellular. Of the extracellular fluid, a fourth is represented by plasma (5 per cent of total body weight) and three-quarters represented by the interstitial fluid (15 per cent of total body weight) (Fig 6.1).

Sodium is the principal cation of the extracellular fluid. Only two per cent of sodium is intracellular. About 55 per cent of body sodium is present in a non-exchangeable form deep in the matrix of bones and cartilage. Exchangeable sodium is present in the plasma; interstitial fluid and intracellular fluid (40 mEq/kg of body weight), and alteration in body sodium is synonymous with change in exchangeable sodium.

The normal subject has dietary sodium intake of 150–200 mEq and the serum sodium is maintained within a narrow range of 140–144 mEq/l. The normal adult requirement of water to cover obligatory losses such as sweat, urine, gastrointestinal secretions, is 800–1000 ml. The minimum amount of water required for the kidneys to excrete all the daily solutes is about 500 ml (with maximum renal concentration ability).

Water moves freely across all cellular membranes and therefore water concentration in all body fluid compartments is equal. Major solutes of the body, however, do not share this freedom of movement. Solute concentration is measured in terms of 'osmoles'. The term 'osmole' refers to the relationship between molar concentration and osmotic activity.[1]

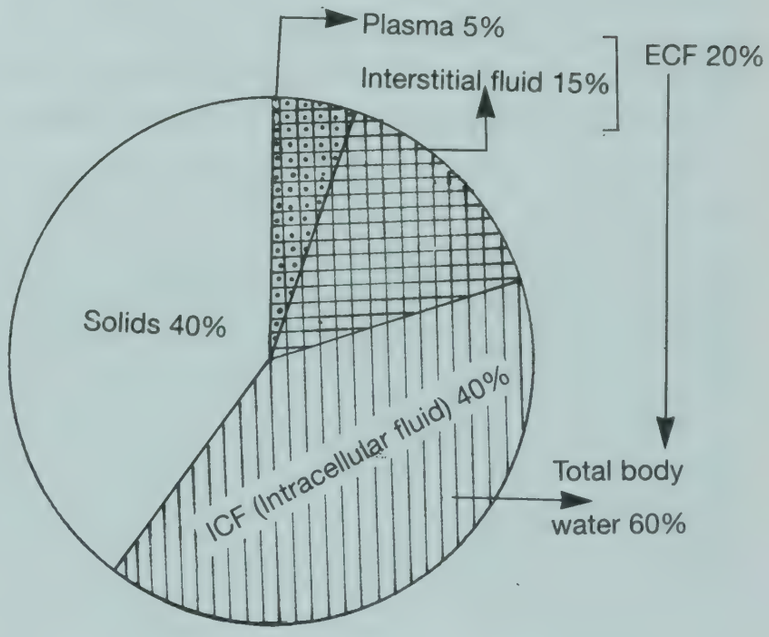


Fig 6.1 Distribution of body water. Percentages refer to percentage of body weight

ICF	ECF
Na^+ : 12 mEq/l	142 mEq/l
K^+ : 150 mEq/l	4.3 mEq/l

Fig 6.2 Distribution of major cations in body water

[1] osmolality = molar concentration × number of particles per mole on ionisation.
Thus, since glucose in solution provides one particle per molecule, one mole of glucose yields one osmole. Since one molecule of NaCl dissociates into two particles (Na^+, Cl^-), one mole of NaCl yields two osmoles. Osmole per kilogram of *water* is termed osmolal. Osmole per kilogram of *solution* is termed osmolar.

Solutes are so distributed across cell membranes that there are equal net osmolal concentrations is each compartment. Intracellular osmolality is, therefore, equal to extracellular (and plasma) osmolality and is maintained over a narrow range of 285–295 mOsm/l.

When there is a loss of water or solute, there may be a net change in osmolality of the extracellular fluid (unless both are lost in equal proportions). The change in the osmolality of the extracellular fluid is associated with a net movement of water into or out of a cell. The result is a tendency to change cell volume. When such processes are acute, clinical manifestations can be dramatic due to acute cellular shrinkage or acute cellular swelling. When the processes are chronic, compensatory mechanisms come into play to prevent a change in cellular volume. Thus, cellular shrinkage is minimised by accumulation within the cell of 'unidentified solutes' which draw water into the cell due to their osmolality—the so-called 'idiogenic osmoles'. Similarly, cellular swelling is offset by the loss of intracellular solutes (loss of potassium chloride from cells).

Thus, disturbances in composition of extracellular body fluid may be either 'volume' changes or 'osmolarity' changes and frequently both together. Volume changes can be identified as 'expansion' or 'contraction' and solute compositional changes can be described as isotonicity (no change in osmolality), hypotonicity (decrease in osmolality) or hypertonicity (increase in osmolality). Plasma osmolality represents extracellular fluid osmolality and can be measured with an osmometer (true plasma osmolality). Plasma osmolality can also be estimated (estimated plasma osmolality) by measuring the concentration of the most prevalent osmotically active solutes.

$$\text{Osmolality (mOsm/kg)} = 2\,[Na^{+}\,(\text{mEq/l}) + K + (\text{mEq/l})] + \frac{[\text{BUN (mg/dl)}]}{2.8} + \frac{[\text{Blood glucose (mg/dl]}}{18}$$

If measured plasma osmolality is more tha estimated plasma osmolality (a difference o more than 10 mOsm/kg), it suggests that th plasma contains significant quantities o unmeasured osmotically active solutes such a mannitol, ethanol or methanol.

The two prime mechanisms which regulat body fluid volume and tonicity are thirst and th antidiuretic hormone (ADH) secreted by th posterior pituitary gland. Thirst primaril regulates fluid intake and is stimulated both b volume concentration as well as an increase i plasma osmolality. The release of ADH is als mediated both by volume contraction (volume sensitive receptors) and an increase in plasm osmolality (osmoreceptor-mediated). It is, hov ever, not essential that volume changes an osmolality changes go hand in hand or even i the same direction. Thus volume contraction ca be associated with a decrease in serum osm lality (for example, Addison's disease or chron diarrhea) under these circumstances. AD release is dominated by osmoreceptor-mediate stimuli (in this case leading to inhibition ADH release) unless the volume contracti exceeds five per cent of body weight. If volun deficits are of this magnitude or more, th influence of volume sensitive receptors ca override that of the osmoreceptors. Th osmoreceptors are, however, more sensitive an respond to changes in plasma osmolality as sm as 0.5 per cent.

Clinical estimates of volume status are bas on examination of postural changes in blo pressure, body weight, the state of the sk (moisture and turgor) and distension of t jugular veins. Thus, expansion of extracellul fluid volume is evident as weight gain (change over one per cent being deemed significan peripheral edema and 'full' jugular vei Volume contraction is evident as orthosta hypotension, weight loss, poor skin turg absence of axillary sweat, sunken eyes and d tongue (depending, of course, on the amount water deficit). Orthostatic hypotension is t

most sensitive clinical index of hypovolemia in adults.

Serum sodium, however, is not an accurate guide to volume status or tonicity; it reflects only the relationship between total body water and sodium. The hematocrit does not provide an accurate measure of volume expansion or contraction. A 20 per cent deficit of body water (without any solute deficit) is associated with an elevation of hematocrit of only one per cent. The presence of an elevation in hematocrit is strong evidence for the coexistence of a sodium deficit, in addition to a volume deficit.

Clinically relevant changes in body water content (volume) or sodium (main determinant of extracellular tonicity being the principal extracellular cation) are one of six types (Table 6.1).

Hypotonic contraction refers to a disorder with volume deficit as well as sodium loss in excess of 400 mEq (resulting in a decrease in serum osmolality). Isotonic contraction also describes deficits of both water and sodium but the sodium deficits are overall less, being in isotonic proportions with water. Hypertonic contraction represents loss of water in excess of solute loss.

Table 6.1 Classification of changes in plasma volume and osmolality

Type of disturbance	*Description*	*Serum sodium*	*Serum osmolality*	*Clinical example*	*Therapy*
1. Hypotonic contraction	↓ body water ↓↓ sodium	↓ ↓	↓ ↓	Addison's disease, chronic diarrhea, diuretic abuse, hot weather with inadequate intake of sodium	i.v. isotonic (0.9%) sodium chloride oral salt repletion
2. Isotonic contraction	↓ body water ↓ sodium	n	n	diarrhea (acute), hot water with adequate salt repletion, intestinal obstruction	i.v. isotonic (0.9%) sodium chloride
3. Hypertonic contraction	↓ body water ↓ sodium	n or ↑	↑	diabetes mellitus, diarrhea with poor water retention, hot weather with poor water repletion	i.v. 2.5% dextrose in 0.2 % sodium chloride **
4. Hypotonic expansion	↑↑ body water n or ↑ sodium	↓	↓	syndrome of inappropriate ADH secretion (SIADH), congestive heart failure*, cirrhosis*	restrict fluids (for SIADH) diuretics plus converting enzyme inhibitors for congestive heart failure,
5. Isotonic expansion	↑ body water ↑ sodium	n	n	congestive heart failure, cirrhosis, nephrotic syndrome	restrict fluids, diuretics
6. Hypertonic expansion	↑ body water ↑↑ sodium	↑	↑	mannitol administration, administration of 5% dextrose in 0.9% sodium chloride to uncontrolled diabetic	restrict fluids, diuretics, stop offending therapy

* These conditions can cause isotonic or hypotonic expansion.

** Fluid choice dictated to keep osmolality of fluid being infused below that of plasma osmolality

Hypotonic expansion refers to the retention of excess water. This occurs either with sodium deficit (such as in the syndrome of inappropriate ADH secretion) or even with sodium excess (water excess exceeding sodium excess as in congestive heart failure). Isotonic expansion describes retention of both water and sodium in isotonic proportions. Hypertonic expansion is retention of both water and sodium with the latter being more than the former. It is virtually always iatrogenic (Table 6.1).

Treatment of solute deficits is, therefore, guided by the concomitant state of replenishment of total body water. Thus, hyponatremia cannot be treated simply with salt repletion. If it occurs with volume contraction, then therapy is aimed at salt and water repletion. If it occurs with volume expansion (as in SIADH), a restriction of fluid intake will suffice.

When water or sodium is to be replaced the amount required can be calculated thus:

$$\text{Na deficit} = (144 - \text{observed Na}) \times 0.6 \times \text{body weight (kg)}$$

$$\text{Water deficit} = (1 - 144/\text{observed Na}) \times 0.6 \times \text{body weight (kg)}$$

The choice of fluid for replacement is guided by serum osmolality (Table 6.2).

POTASSIUM

Normal physiology

Potassium is the major intracellular cation in the body. The total body content of potassium is about 3000 mEq. Of this only two per cent (60 mEq) is extracellular. The daily intake of dietary potassium is about 50–100 mEq and this is predominantly excreted by tubular secretion by terminal nephron segments. Factors which enhance potassium excretion include an increased delivery of sodium to the distal tubule, an increased plasma pH and increased aldosterone levels. The distribution of potassium between the intracellular compartment and the extracellular fluid is governed by the cell membrane bound enzyme 'Na^+ K^+ ATPase' which actively transports potassium into the cells. Insulin, epinephrine and a rise in plasma pH all promote cellular uptake of potassium. At a rough estimate, a rise of plasma pH by 0.1 unit decreases serum potassium by 0.6 mEq/l and a fall of plasma pH by 0.1 unit elevates serum potassium by a similar amount. The potassium concentration of extracellular fluid is regulated between 3.5 and 5 mEq/l normally.

Potassium plays a vital role in skeletal and smooth muscle contraction, conduction of nerve impulses, enzyme action and cell membrane function. The clinical consequences of potassium deficits or excess are therefore referable to changes in the function of the excitable tissues. Thus, hyperkalemia partially depolarises electrical tissues at rest by reducing the K_i/K_o[1] ratio. It also decreases the rate of sodium entry into the cells so that the net effect is to make tissues refractory to excitation. Hypokalemia produces hyperpolarisation of membranes and reduced excitability (Table 6.3).

Table 6.2 Osmolality of parenteral fluids

Fluid	*Osmolality (mOsm/kg H_2O)*
Plasma	285–295
5% dextrose	280
0.9% (0.155 molar) NaCl	280
5% dextrose in 0.9% NaCl	560
2.5% dextrose	139
2.5% dextrose in 0.2% NaCl	207

Hypokalemia

Hypokalemia is defined as a serum potassium concentration of less than 3.5 mEq/l.

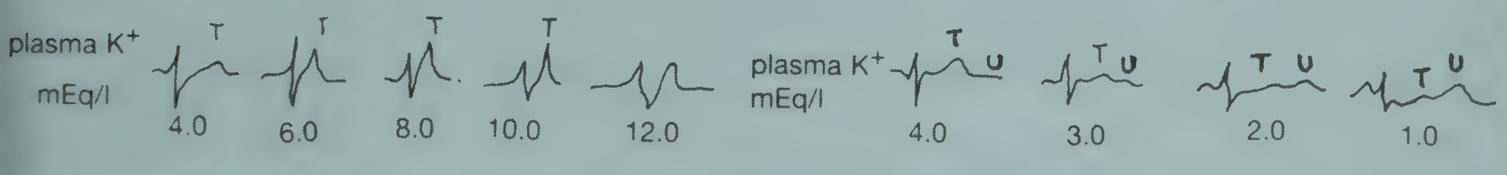
Etiology The causes of hypokalemia are shown in Table 6.4.

Clinical features The clinical symptomatology depends partly on whether the potassium deficit are acute (when the presentation can be sudden

[1] Refers to $K_{intracellular}/K^+_{outside\ the\ cell}$

Table 6.3 Pathophysiology of potassium disorders at the cellular level

Hyperkalemia	*Common clinical features*	*Hypokalemia*
Initially • reduced resting transmembrane potential (E_m) = –61 log $\frac{K_i}{K_o}$ = partial depolarisation, • unchanged threshold potential, • increased excitability of conducting tissue (initially) • decreased rate and amplitude of depolarisation (reduced Na+ entry) • accelerated repolarisation (increased K^+ permeability) *Finally* • Inexcitability of conducting tissue	**neuromuscular** muscle cramps restless legs muscle weakness respiratory insufficiency decreased deep tendon reflexes paralysis respiratory arrest **cardiac** conducting abnormalities atrial arrhythmias ventricular arrhythmias **smooth muscle** nausea vomiting abdominal pain gastric atony ileus urinary retention	*Initially* • Increased resting transmembrane potential (E_m) = hyperpolarisation decreased excitability of conducting tissue • increased velocity of conduction *Finally* • decreased E_m (reduced K^+ permeability) • decreased velocity of repolarisation (reduced K^+ permeability) • prolonged relative refractory period (increased risk of arrhythmias)



or dramatic) or chronic, as well as on the degree of potassium deficit. At serum potassium concentrations of 2–2.5 mEq/l, muscular weakness becomes evident and deep tendon reflexes are diminished. If untreated this can progress to areflexic flaccid paralysis with respiratory distress. Smooth muscle involvement of the intestines manifests as paralytic ileus. Impaired mentation with drowsiness, apathy or even coma may be present. Severe deficits of potassium may precipitate rhabdomyolysis and myoglobinuria. Hypokalemia-induced impaired renal tubular ability to concentrate urine can lead to reversal of the diurnal pattern of urine excretion manifesting as nocturia and polyuria. Electrocardiographic manifestations are usually evident at serum potassium concentrations less than 3 mEq/l. The T-wave amplitude diminishes, U-waves appear, the Q-T interval prolongs and the S-T segment appears depressed. Further lowering can result in ectopic atrial and ventricular activity, atrioventricular block and ultimately in ventricular fibrillation.

Table 6.4 Causes of hypokalemia

Inadequate intake
- starvation
- prolonged use of intravenous fluids lacking potassium

Increased loss
- Gastrointestinal loss
  - vomiting[1]
  - diarrhea
  - villous adenoma
- Renal loss
  - diuretics
  - mineralocorticoid excess
  - tubular defects (renal tubular acidosis, Fanconi syndrome)
  - Bartter syndrome
  - metabolic alkalosis

Hypokalemia with no deficit
(extracellular fluid compartment → intracellular compartment shift)
- acute alkalosis
- hypokalemic periodic paralysis
- insulin therapy
- vitamin B_{12} therapy for megaloblastic anemia

[1] The hypokalemia associated with vomiting is actually related to renal loss of potassium produced by secondary hyperaldosteronism and loss of bicarbonate in the urine. The potassium content of upper GI secretions is small (10 mEq/l). Diarrheal stools, however, contain enough potassium (30 mEq/l) to directly account for potassium deficits.

Treatment The treatment consists of identifying the underlying mechanisms (Fig 6.3) and providing potassium replacement. As a rough guideline a decrease in serum potassium of 1 mEq/l indicates a deficit of potassium of 200–300 mEq. When the serum potassium is less than 2.5 mEq/l, the potassium deficit may range from 400–1000 mEq. Potassium replacement is always preferable by the oral route unless therapy is emergent. Initially 120 mEq of potassium may be given as a 10 per cent solution of potassium chloride in orange juice if renal function is normal. Further therapy is guided by serum potassium levels and supplements of 100 mEq potassium can be given daily (besides dietary potassium). If renal function is impaired, the initial oral potassium dose is restricted to 80 mEq and daily potassium supplements thereafter restricted to 40 mEq.

If intravenous administration is required, potassium chloride is added to the intravenous fluid at a concentration not more than 40–60 mEq/l and no more than 10–20 mEq potassium administered in an hour. Careful electrocardiographic monitoring is mandatory.

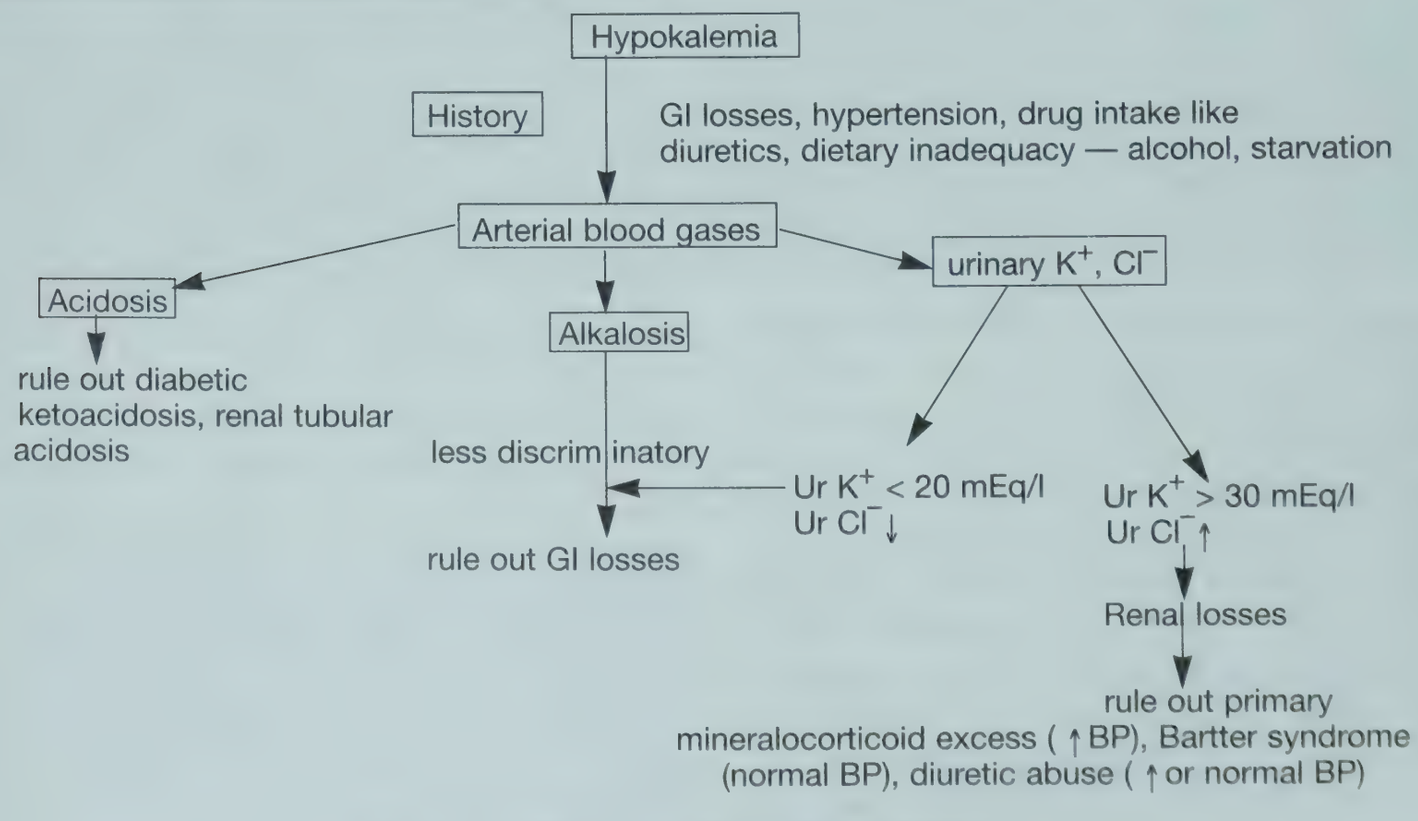


Fig 6.3 Approach to a patient with hypokalemia

Hyperkalemia

Hyperkalemia is defined as a serum potassium level more than 5.0 mEq/l.

Etiology The causes of hyperkalemia are shown in Table 6.5.

Clinical features The neuromuscular manifestations of hyperkalemia are clinically indistinguishable from those of hypokalemia. Thus, weakness or a flaccid areflexic paralysis, paralytic ileus and respiratory distress may be encountered. The electrocardiographic features are, however, distinctive. Amongst the earliest features (at a serum potassium level of 6 mEq/l) is peaking of T-waves (tall 'tented' and symmetrical). This is followed by a decrease in amplitude of P-waves, prolongation of the P-R interval and QRS duration. At serum potassium levels of 9 mEq/l a classical 'sine wave' pattern may be evident leading ultimately to asystole.

Table 6.5 Causes of hyperkalemia

Diminished renal excretion
- reduced glomerular filtration
- acute renal failure
- chronic renal failure[1]
- reduced tubular secretion
- adrenocortical insufficiency
- potassium sparing diuretics
- hyporeninemic hypoladosteronism

Due to shifts
- (intracellular fluid compartment → extracellular fluid compartment)
- acidosis
- cell destruction (trauma, burns, rhabdomyolysis, hemolysis)
- hyperkalemic periodic paralysis
- use of muscle depolarising agent
- succinylcholine

Artefactual[2]
- thrombocytosis
- leukocytosis

[1] Usually occurs late when when GFR has fallen below 5 ml/min

[2] In these conditions, 'plasma' potassium is normal though 'serum' potassium is elevated.

Table 6.6 Therapy of hyperkalemia (graded according to rapidity of effect)

*Modality***	*Onset of action*	*Duration of effect*	*Mechanism*	*Comments*
1. Calcium gluconate	Immediate	30–60 min	membrane antagonism	increased E_T* increased sodium channels faster conduction
2. Sodium bicarbonate	10–30 min	2 hours	transcellular redistribution	decreases ionized calcium level risk of sodium overload
3. Glucose and insulin	15–30 min	during infusion	transcellular redistribution	risk of hypo/hyperglycemia
4. Kaliuretic/diuretic agent (furosemide)	10–20 min	3–6 hours	excretion (renal)	requires renal function
5. Cation-exchange resin (sodium polystyrene sulfonate)	1–2 hours	4–6 hours	excretion (fecal)	may cause vomiting, fecal impaction, sodium overload
6. Hemodialysis	Immediate	during dialysis	removal	risk delay in treatment
7. Peritoneal dialysis	Gradual	during dialysis	removal and transcellular redistribution	K^+ removal < 5 mEq/hr

* E_T = threshold potential
** for doses see text

Treatment The emergency treatment of life-threatening hyperkalemia is aimed at immediate reversal of the electrophysiologic membrane — effects of hyperkalemia. This is achieved with intravenous administration of 10–20 ml of a 10 per cent solution of calcium gluconate over a period of 10–20 minutes with electrocardiographic monitoring throughout. If the hyperkalemia is not immediately life-threatening, treatment is aimed at achieving a shift of potassium into the cells over the next few hours. This is achieved with the administration of either an intravenous bolus of 50 ml of 50 per cent glucose solution with five units of regular insulin or by an infusion of 500 ml of 20 per cent glucose solution over six hours (with 5–10 units regular insulin). Alternatively, about 40–140 mEq of a 1.26 per cent solution of sodium bicarbonate (equivalent of 1–3 ampoules) can be administered intravenously over a period of one hour.

A slower removal of potassium is achieved with the use of sodium based cation exchange resins such as sodium polystyrene sulphonate. These resins exchange 2 mEq sodium for 1 mEq of potassium and can remove 50–100 mEq of potassium over a six-hour period. These resins are combined with sorbitol to prevent constipation and therefore carry the hazard of sodium overload in subjects with renal impairment.

If hyperkalemia is refractory to the above measures, especially in the setting of poor renal function, dialysis may be indicated. Hemodialysis is more than twice as efficient in removing potassium as compared to peritoneal dialysis.

KEY CONCEPTS

- Water constitutes about 60% of body weight; two-thirds is intracellular and the rest is extracellular (ECF). Plasma comprises 25% of ECF. Body water content is tightly regulated by thirst mechanisms, ADH and the kidneys. Potassium is mainly intracellular, while sodium is predominantly extracellular.
- Water deficits often occur concurrently with sodium deficits. Generally, half the deficit and maintenance and ongoing losses are corrected over the first 24 hours; half of this 24 hour replacement is provided over the first 8 hours.

Hyponatremia

- <135 mEq/L; may be *hypotonic* (P_{osm}<280 mOsm/ kg; relative water excess/dilutional: CHF, cirrhosis, nephrosis; hypo volemic: GI/renal losses; euvolemic: SIADH), *hypertonic* (P_{osm}>295 mOsm/kg; hyperglycemia, mannitol infusion), or isotonic (P_{osm} 280–295 mOsm/kg; artifact such as due to hypertriglyceridemia).
- Symptoms are due to cerebral edema; include lethargy, headaches, seizures.
- Diagnostic approach includes assessment of ECFV, P_{osm}, U_{osm}, and U_{Na}.
- Increased P_{osm} indicates accumulation of non-sodium osmole (e.g. glucose). If P_{osm} is normal, exclude increased TG. If P_{osm} is reduced, assess U_{osm}. A value of U_{osm} <100 mOsm/kg suggests primary polydipsia. If U_{osm} is >100 mOsm/kg, reduced renal diluting ability is likely. Assess ECFV below.
  - Reduced ECFV with U_{Na} <10 mEq/L: hypovolemia such as GI losses. Reduced ECFV with U_{Na} >20 mEq/L: renal losses (Addison's disease, diuretics, osmotic diuresis).
  - Increased ECFV with U_{Na} <10 mEq/L: dilutional, such as CH. Increased ECFV with U_{Na} >20 mEq/L: renal failure.
  - Normal ECFV and U_{Na} >20 mEq/L: SIADH, endocrinopathy (hypothyroidism, Addison's), hypokalemia, diuretics.
- The treatment depends on the severity and cause. Dilutional: restrict water intake. Normal saline is preferred for the replacement of volume losses.

Hypernatremia

- >145 mEq/L; may be due to *pure water loss*, *hypotonic fluid loss*, or *solute gain*.

- ➢ Symptoms are neurologic and reflect cellular dehydration: confusion, lethargy, seizures, coma.
- ➢ Assess ECFV, U_{osm}, and U_{Na}. Normal ECFV suggests pure water deficit, whereas reduced ECFV indicates hypotonic deficit.
  - * Reduced ECFV, U_{Na} <10 mEq/L, U_{osm} >700 mOsm/kg: extrarenal losses (GI).
  - * Reduced ECFV, U_{Na} >20mEq/L, U_{osm} <700 mOsm/kg: renal losses (diuretics)
  - * Normal ECFV, U_{osm} <700 mOsm/kg: Diabetes insipidus. Normal ECFV, U_{osm}>700 mOsm/kg: extrarenal losses (GI)
  - * Pure water loss: replace water; hypotonic losses: replace volume. *Correct gradually.*

Hypokalemia

- ➢ <3.5 mEq/L; can be due to *redistribution* (intracellular shift: alkalosis, insulin, β agonists), *renal losses* (tubular disorders), and *extrarenal losses* (GI).
- ➢ Symptoms include weakness, paresis, ileus, constipation, polyuria, polydipsia; ECG features include ST depression with U waves; there is a predisposition to ventricular ectopy and digitalis toxicity
- ➢ ABG, U_K, U_{Cl} are helpful. U_K<20 mEq/d indicates: GI losses (diarrhea, villous adenoma). If U_K is >20 mEq/d, look at ABG for acidosis vs alkalosis.
  - * Acidosis suggests renal tubular acidosis, diabetic ketoacidosis, or Diamox intake.
  - * If there is alkalosis with hypertension: Conn syndrome, Cushing syndrome, renin-secreting tumour.
  - * If there is alkalosis with normal BP: diuretic use, Bartter syndrome likely.
- ➢ Treatment consists of potassium replacement. A decrease of 1 mEq/L of serum potassium indicates 200 mEq body deficit. A serum value below 2.5 mEq/L, indicates 400–1000 mEq deficit.

Hyperkalemia

- ➢ >5.0 mEq/l; causes include *redistribution* (acidosis, digitalis, β blockade), *renal retention*, or *spurious* (hemolysis, tight tourniquet, leuco/thrombocytosis)
- ➢ Symptoms include flaccid paralysis, cardiac arrest. ECG features include (in sequence): tall peaked T waves—->wide QRS, nodal and ventricular arrhythmias—->flat P, sine wave pattern.
- ➢ Measure renal functions to exclude renal failure. If renal functions are normal, measure aldosterone.
  - * Low aldosterone: Addison's hyporeninemia
  - * Normal or elevated aldosterone: tubular disorders, potassium-sparing diuretics.
- ➢ Non-emergent treatment: potassium-exchange resins. Emergency treatment: calcium gluconate, sodium bicarbonate, glucose-insulin infusion, dialysis.

7

Imaging in Medical Disorders

Imaging refers to the visualisation of the organs and structures in the intact patient. Energy in the form of ultrasound waves, X-rays or particles emitting isotopes, is sent into the body either as an external beam (ultrasound waves, X-rays) or by introduction into the circulating blood, cerebrospinal fluid (CSF) or inhaled air (isotopes). The X-ray energy passing through the area of interest (*transmitted* energy) is recorded to yield conventional X-ray films, fluoroscope images on a television monitor, cine records on continuously moving film, or digital values which can be stored in a computer and reprocessed to give the kind of image (in terms of contrast, size, angle) required. The computer is indispensable for techniques such as CT scanning (computerised tomography) and DSA (digital subtraction angiography).

The ultrasound energy *reflected* from the organ of interest is used to yield an ultrasound image. Thus, all ultrasound images are records of 'echoes' – echograms – although the term is commonly used while imaging the heart or blood vessels (echocardiography).

The *energy emitted* from isotopes is recorded using either a simple gamma camera (conventional isotope imaging) or is computerised to yield emission tomograms.

CONVENTIONAL ROENTGENOGRAMS

X-rays

Worldwide, this is still the most commonly used imaging technique. High energy photons—X-rays—pass through the body and impinge on a photographic film which is processed to give the image. The required machinery is relatively cheap and easy to handle and maintain. The silver halide used in the film is expensive. In MMR (mass miniaturised radiography) special lenses reduce size of the image. The term 'mass' refers to the fact that the technique was developed for the radiological screening of large populations for pulmonary tuberculosis.

Plain X-rays are excellent for visualising the bones and lungs. Radio-opaque contrast media (barium, urografin) may be introduced into the body either alone (contrast study) or in combination with a radiolucent contrast medium, usually air, to perform a 'double-contrast study'. These techniques are discussed in the individual sections.

X-rays should not be performed as a 'routine'. The routine chest X-ray and skull X-ray have been shown not to be cost-effective.

If a patient with a serious head injury is brought to a centre which has a CT scan, then with the same X-ray exposure required for a skull X-ray, both the skull bones and the brain can be jointly assessed in a CT scan.

Tomography

In this technique, the X-ray beam and recorder are rotated through an arc which is so chosen that the 'plane of interest' always lies within the transmission path of the beam, while the other planes lie in the transmission path along only a

part of the arc and hence are blurred out. Conventional tomograms are used to delineate the bones at the atlantoaxial joint and in a few other situations.

Computerised Tomography

In this technique, an X-ray source and a recording device are mounted on the opposite ends of a curved arm. The patient is placed in the path of the thin beam. The arm rotates so that the beam 'sees' the required cross-section from every angle. The transmitted values stored in the computer are processed to yield a remarkably detailed picture of the bones and soft tissues in that cross-section. Then, the table moves to bring the next cross-sectional slice in the path of the beam. The absorption values of various tissues can be read out in 'Hounsfield units', so called after one of the inventors of the CT scan.

The first generation scanners took nearly five minutes to image one slice and the resolution (number of image units or 'pixels' per slice) was low. The latest ultrafast CT scans can image a slice in 20 seconds.

Advantages of CT It has revolutionised the imaging of almost all the organs including the skull, brain, lungs, abdominal and pelvic organs. Fat appears very dark (low absorption coefficient) while calcified tissues appear very bright (high absorption coefficient). Blood also appears white.

A contrast agent can be given (barium, urografin) to improve resolution. Tissues which take up the contrast material (contrast-enhancing) become more white (develop higher absorption coefficients).

ANGIOGRAPHY

The vascular tree is imaged by injecting a bolus of contrast followed by a rapid sequence of X-rays. These X-rays show in succession the arterial phase, the capillary phase and the venous phase.

Technique Catheters are introduced into the vessel of interest using a percutaneous puncture technique (Seldinger technique). The site of puncture is usually the femoral vessels in the groin. If the catheter is maneuvered into a branch of the aorta (for example, the common carotid or the celiac trunk) before injection of the dye, it is called *selective* angiography. When a second order branch is catheterised (for example, the hepatic artery) it is called *superselective* angiography.

Uses Angiography is used

1. to study the chambers and valves of the heart;
2. to study the branching pattern and structure of the vessels (detecting occlusion due to atheroma, arteritis);
3. to study vascular malformations such as aneurysms and arteriovenous malformations (AVMs);
4. to assess, preoperatively, the blood supply to a tumour, to enable better planning of surgery; and
5. as a prelude to interventional radiology procedures which can be done in the same sitting. These techniques are described later.

Digital Subtraction Angiography (DSA)

The principles and procedure of DSA are outlined in Fig 7.1.

The transmitted X-rays strike a fluoroscopic screen to form an image. Light intensity at a point is converted into a digital value according to a predetermined scale. The digital values for the mask are stored in the computer which does the subtraction and instantaneously displays the final images.

The advantages of DSA are that

1. It is faster than conventional angiography as one does not have to wait for the X-ray films to be developed to see what has been imaged.
2. There is no obscuration of vessels by overlying bone or soft tissue. Hence the resolution is better.

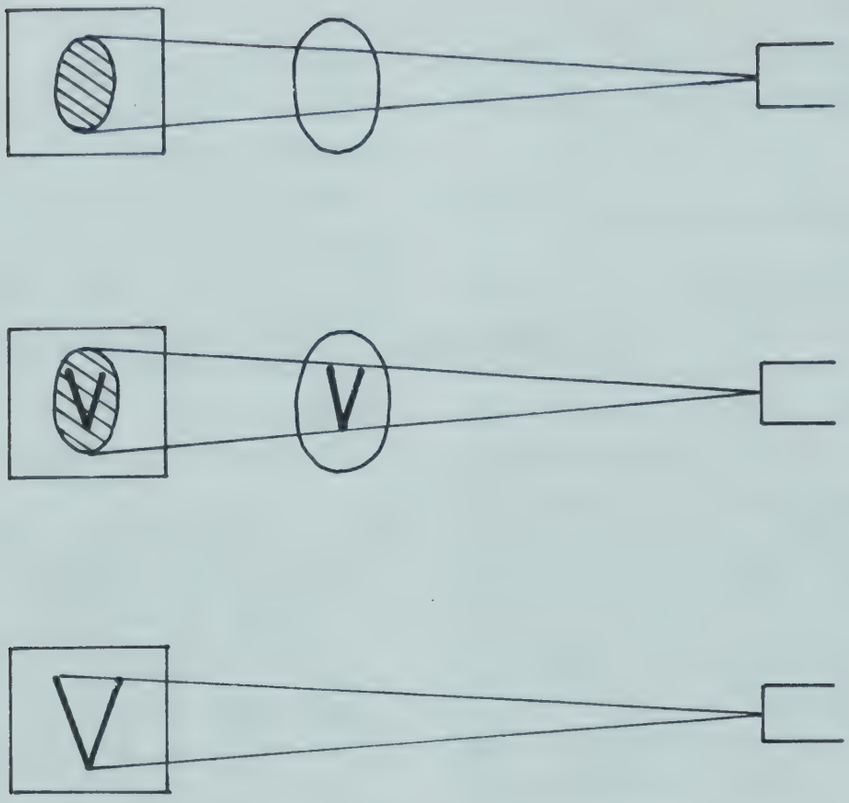


Fig 7.1 Principles and procedure of DSA

3. Because of this, lower doses of contrast are required per image as compared to the conventional angiogram.

A disadvantage is that in the final photographic record, the relationship of the vessel to bony landmarks is not seen.

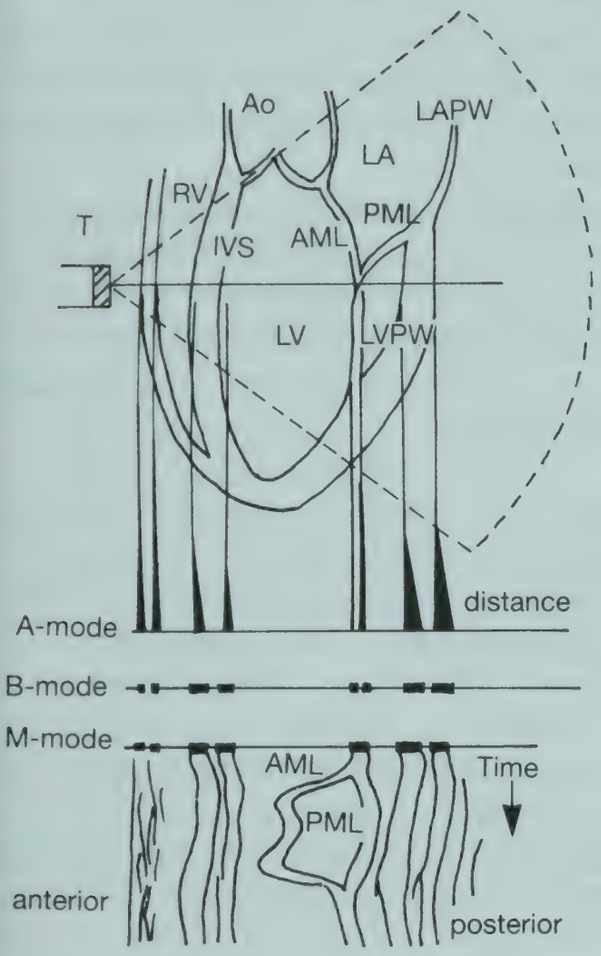
Types of DSA In *intravenous DSA (IV-DSA)* a contrast agent is injected into a forearm vein. The advantage of this technique is that arterial catheterisation (with its associated risks) is not required. However, it is not widely used today because: 1) resolution is low especially in the neck (carotid vessels) where the image is further degraded by respiratory movement artefacts, and 2) a high dose of contrast is required. This may be dangerous in patients with cardiac problems who may go into congestive cardiac failure.

Intraarterial DSA is preferred to conventional angiography. Its advantages have been discussed earlier. Its higher resolution means that time-consuming and risky supraselective catheterisation is rarely required.

ULTRASOUND IMAGING

A piezo-electric crystal mounted on a 'transducer' both emits ultrasound waves and records the reflected echoes. This transducer is held in the operator's hand and can be moved as required. The frequency of the ultrasound waves used varies from 2 to 12 megahertz. The lower frequency high energy waves can penetrate better (image deeper structures) but their resolution is less. A suitable medium–water or 'jelly'–lies between the transducer and the skin. Structures may be 'echolucent' (such as the fluid in a cyst) or 'echodense' such as gallstones. Highly echodense structures cause areas of 'acoustic shadowing' behind them.

The ultrasound image can be displayed in various modes–A mode, M mode and 2D mode (Fig 7.2). The advantages of ultrasound are that it is cheap, imaging can be done in any plane and in 'real time'. Most importantly, ultrasound waves are harmless even to a developing fetus, so that any number of repeat studies can be done.



2D echocardiography involves moving the ultrasonic beam in a sector so that a pie-shaped slice of the heart is interrogated.

Amplitude or A-mode

The echo signals are shown on the oscilloscope screen in the form of vertical signals along the horizontal axis of the screen. The position from left to right represents an increasing distance between transducer and reflecting boundaries. The amplitude of the echo signals represents the intensity of the reflected sound.

Brightness or B-mode

In this display the A-mode echoes are converted to dots, the brightness of which is related to the intensity of reflected sound.

Time-motion or M-mode

If the B-mode display is swept at a constant speed from bottom to top over the oscilloscope screen, the motion pattern of the various heart structures is visualised. This presentation is called M-mode and may be recorded with polaroid film. The electrocardiogram is recorded simultaneously on the film.

Fig 7.2 Schematic cross–section of the heart showing the structures through which the sound beam passes when the transducer (T) is placed in the third or fourth left intercostal space. RV–right ventricle, IVS–interventricular septum, LV–left ventricle, AML–anterior mitral leaflet. PML–posterior mitral leaflet. Ao–aorta, LA– left atrium, LVPW–left ventricular posterior wall, LAPW–left atrial posterior wall. The four types of oscilloscope display are shown.

The disadvantages of ultrasound are that the accuracy of the imaging depends greatly on the skill of the operator (operator-dependent), the resolution is lower than for other techniques such as CT and MRI and a suitable 'viewing window' must be obtained which does not require the sound beam to pass through air or bone.

Ultrasound imaging is very useful for imaging the heart, abdominal and pelvic organs (the last through a full bladder) and the fetus and placenta *in utero*. Specialised techniques include imaging the neonatal brain through the anterior fontanelle, intraoperative imaging of deep-seated tumours and cysts using a probe on the surface of the brain, imaging of the blood vessel at the base of the brain through the orbital roof plate (transcranial doppler) and intracavitary imaging where probes are introduced into body cavities. Intracavitary imaging may be transrectal (to visualise the prostate and rectum), endovaginal (for pelvic organs), transesophageal (esophagus, stomach, posterior mediastinum and atria of the heart) or intravascular (vessels of the heart)

MAGNETIC RESONANCE IMAGING (MRI)

In magnetic resonance imaging (MRI) which was earlier called nuclear magnetic resonance (NMR), the magnetic energy emitted by atomic nuclei (usually the hydrogen nuclei H^+ or

protons) placed in an external magnetic field is used to image an organ in vivo.

Principle All atomic nuclei carry a net positive charge. They also have an inherent property of 'spin' around a central axis. It is a law of physics that when an electrically charged particle moves, it sets up a magnetic field around it. This field has a net magnetisation vector. When these atomic nuclei are placed in a powerful external magnetic field, they align themselves along the magnetisation vector of the external field (like iron filings near a magnet). If the external field is now turned off, the nuclei return gradually to their original random orientations. In this process, the magnetic energy they had absorbed to align themselves in parallel is emitted. This energy is detected and used to form an anatomical image.

Process At the heart of the MRI scanner is a powerful electromagnet of 0.2–1.5 tesla (1 tesla = 10^4 Gauss; 1 Gauss is about 1.75 times the earth's magnetic field).

The imaging characteristics of a tissue depend on the number of protons it has (proton density), the interaction of the protons with adjacent heavier atomic nuclei (T_1 or spin-lattice relaxation time) and the interactions between adjacent protons (T_2 or spin-spin relaxation time).

The same tissue looks different if imaged according to its T_1 characteristics (T_1-weighted image) or according to its T_2 characteristics (T_2-weighted image). Thus, in an MR scan of the brain, the CSF (cerebrospinal fluid) looks dark (hypointense) in a T_1-weighted scan and bright (hyperintense) in a T_2-weighted scan.

Magnetic fields of the required strength, duration and direction are generated using radio frequency pulses of current. At least two such pulses are used and the angle and time-interval between these pulses are varied to produce different kinds of images. Two commonly used pulse sequences are 1) inversion recovery (T_1-weighted images), and 2) spin echo (T_2-weighted images).

MR resolution is measured in voxels per unit area. Contrast may be enhanced in a T_1-weighted image by intravenous injection of the gadolinium salt–gadopentetate dimeglumine. Tissues which take up the contrast become more hyperintense (white).

In imaging the thoracic structures, respiratory and cardiac gating is required. The respiratory (or cardiac) cycle is broken up into 10–20 units. Corresponding units from adjacent cycles are summed up to yield an image, thus reducing movement artefacts.

Advantages MR scanning involves no radiation exposure. It can yield images in any one of the three dimensions (until recently CT scanners could not do this but very recent napiol CT scanners can). MR images display more detail than CT scans in the imaging of the brain (grey matter–white matter differentiation), spinal cord (imaging modality of choice), cancellous bone and some abdominal organs. It has replaced arthrography in the study of joints.

Disadvantages The scan time is more than that for a CT scan. Hence the patient has to lie still for a longer duration (which is difficult for children and psychiatric or acutely ill patients). The magnetic field can cause dysfunction of cardiac pacemakers, loosening of aneurysmal clips (in the brain) and dangerous movement of metallic particles in the eye. Patients with any of these should not undergo MR scanning. However, dental fillings or metal wires in bones are not contraindications for MR scanning.

Loose metallic objects should not be present within the magnetically shielded scan room. Because of this, the long scan time and the possibility of malfunction in sensitive life support equipment (for example, respirators, ECG monitors), patients who are critically ill are not suitable subjects for MR studies.

Cortical bone calcification and fresh hemorrhage (24–48 hours) which are very clearly seen on a CT scan are not seen in an MR scan

since the water content (proton density) is low (as in bone, calcium) or no different from the surrounding tissue (as in the case of hemorrhage). However, this can also be an advantage. Bone artefacts do not occur in an MR scan.

Finally, MRI is more expensive and less freely available than CT scanning.

Special MRI Techniques

These include:

1. MR angiography
2. MR spectroscopy (MRS)
3. 3-D image display
4. Display of only the surface of a structure, for example, gyral pattern of the brain)
5. Video-imaging (showing the cardiac action or CSF pulsation)

MR angiography

This is a very interesting new technique. Vessels can be seen without the introduction of any catheters or injection of any contrast medium. It is based on the principle of 'velocity dependent contrast'. Within a blood vessel, due to the blood flow, magnetised protons move out of the field under study, while fresh unmagnetised protons keep moving in. Hence, the signals from flowing blood are unique. Only such signals are processed to yield a picture of the blood vessels. As yet, this technique cannot visualise small vessels as well as conventional angiograms or DSA techniques can.

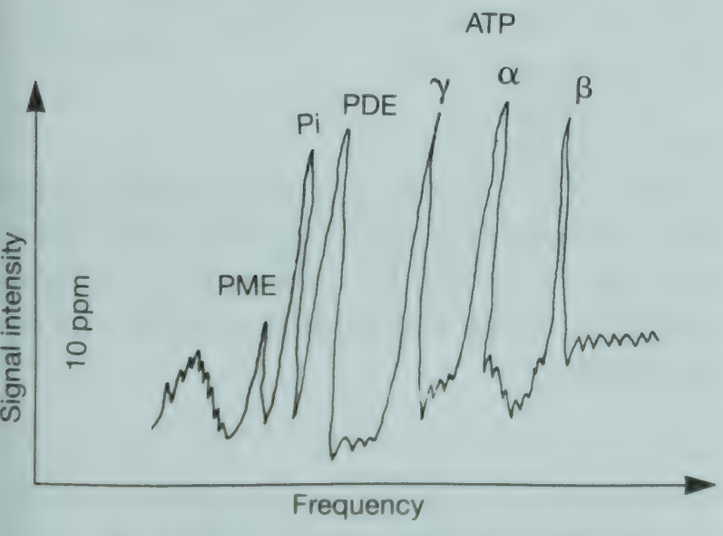


Fig 7.3 ^{31}P spectrum of normal human liver

MR spectroscopy

In this technique, quantitative estimates are made of the concentration of various metabolites within a given volume of tissue. The magnetic signals emitted from the proton (H^+) or three heavier atomic nuclei (^{13}P, ^{13}C and ^{19}F) are used. The frequency of the emitted energy depends on the chemical environment (molecular structure of the compound) within which the atomic nucleus lies. The information obtained is plotted in the form of a spectrum in which signal intensity (related to the concentration of the molecule) varies along the y axis and frequency along the x axis (Fig 7.3).

Uses

1. ^{31}P: In an acidic pH and in hypoxic tissues, the inorganic phosphorus (P_i) peak will be larger and the ATP peaks will be smaller.
2. Carbohydrate metabolism, specially in muscles, can be studied using ^{13}C spectra.
3. ^{1}H spectra can show lactate concentrations (a sensitive index of ischemia).
4. ^{19}F is used to study drug pharmacokinetics (for 5-fluorouracil).

MR spectroscopic imaging (MRSI) and localised MR spectroscopy (LMRS)

Conventional MR images are combined with the results of MR spectroscopy of these areas. Thus areas with high lactate concentration can be superimposed in red on a conventional grey and white MR image of the heart, thus dramatically outlining the area of ischemia or infarction.

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT)

In this technique, a rotating gamma camera acquires data about the distribution of an intravenously injected gamma ray (single photon) emitting radiotracer such as

Technetium-99m (Tc^{99}) or Iodine-123m (I^{123}) and uses this information to construct a computer image in axial, coronal or sagittal planes.

SPECT is the least expensive technique of metabolic imaging and has been called the 'poor person's PET scan'. It is available at several centres in India. The isotopes commonly used are TC-99m HMPAO (hexamethylene propylene amine oxime) and I-123 iodoamphetamine. SPECT can be used to image blood flow and glucose uptake. It can detect infarcts earlier than a CT scan. The resolution is less than in PET (Table 7.1).

Table 7.1 Comparison of PET and SPECT

PET	*SPECT*
More expensive	Cheaper
Isotopes have shorter half-life	Isotopes are long-lasting, easier to handle
Isotopes biologically relevant, e.g., ^{13}C	Isotopes not normally present in body, e.g., ^{99}Tc
Higher resolution	Lower resolution
Quantitative imaging possible	Not possible

POSITRON EMISSION TOMOGRAPHY (PET)

PET is a technique which utilises positron emitting radioisotopes to form an anatomical image (map) of the metabolism, perfusion and pharmacology of various organs in vivo. The map can be in any of the three dimensions (axial, sagittal or coronal section).

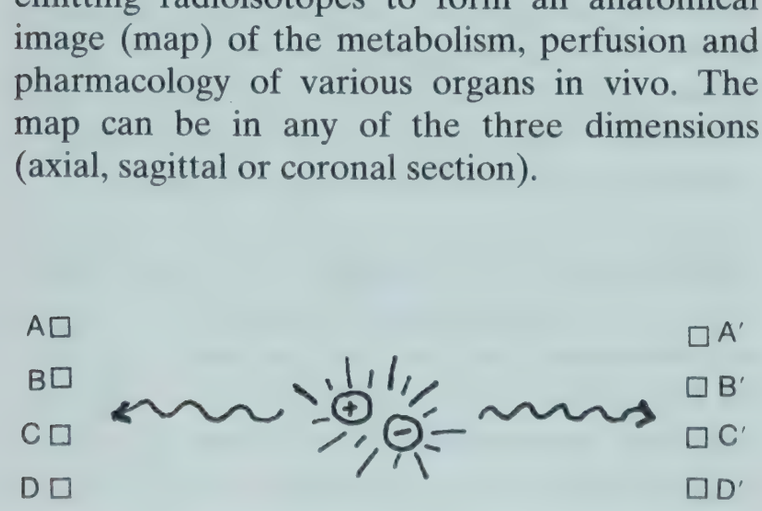


Fig 7.4 Principle of PET

Technique A positron is a positively charged particle with the mass of an electron. It belongs to the group of antiparticles. A positron emitted from an isotope would travel only a very short distance before it meets one of the many electrons within the object being imaged. When a positron collides with an electron, an annihilation reaction occurs. The parent particles disappear and two high-energy photons are given off which travel in opposite directions (Fig 7.4).

When paired detectors at 180° to each other simultaneously detect a photon, an 'event' is recorded. This process is called *coincidence detection.* The resolution (anatomical detail) is greater with PET than with conventional radio isotope techniques involving detection of single photons.

Radioisotopes for PET

Manufacture of position emitting isotopes requires a very sophisticated and expensive 'cyclotron' or a cheaper 'generator'. The cyclotron should be close to the PET site as these isotopes have very short half-lives. The most commonly used isotopes are:

1) Cyclotron-based
   - ^{15}O – Oxygen – half-life 2 minutes
   - ^{11}C – Carbon
   - ^{18}F – Fluorine – half-life 110 minutes
   - ^{13}N – Nitrogen
2) Generato-produced
   - ^{82}Rb – Rubidium
   - ^{68}Ga – Gallium

Using these isotopes as building blocks, most of the biologically useful compounds such as O_2, CO_2 and H_2O can be obtained in positron emitting form and may be used to study normal metabolism.

Uses

Metabolism : Oxygen uptake and glucose uptake can be measured. The isotope used for the latter is FDG (fluorodeoxyglucose). Lactic acid production can be measured.

Perfusion : Blood flow and blood volume can be measured. Intactness of the blood-brain barrier can be assessed. Regional areas of decreased blood flow (hypoperfusion) and increased blood flow (hyperperfusion) can be mapped.

Growth : The rates of protein and DNA synthesis and mitosis can be measured. This is useful in assessing the malignant potential of tumours and their response to therapy.

Bioassays : Accurate quantitative estimations can be made of the amount of a given substance (for example, neurotransmitter-dopamine) within a given volume of tissue (as in the striatumof the brain). The receptor density and tissue uptake of these substances can also be measured.

Thus PET, SPECT and MRSI enable metabolic imaging.

INTERVENTIONAL RADIOLOGY

Under radiological guidance, a variety of interventions can be carried out in the intact patient. Often, these procedures avoid surgery. Hence they are preferred by patients. However, they are often as expensive, require as much skill and are occasionally more dangerous than surgery.[1] Interventional radiology is now a separate, rapidly growing branch of radiology (as distinct from diagnostic radiology). Only a few representative procedures will be described here.

[1] At certain sites which are surgically difficult to approach and in patients who are poor surgical risks, interventional radiology may be the only treatment modality available. It can also be used as an adjunct to surgery and radiotherapy.

Radiologically Guided Biopsy

A special hollow ultrasound probe permits ultrasound guided renal and liver biopsy. This reduced the chances of injuring a vessel or obtaining skeletal muscle instead of kidney in the biopsy.

CT-guided fine needle aspiration cytology is used to diagnose pulmonary lesions as well as pancreatic and other intraabdominal masses.

Endovascular Procedures

Special catheters with inflatable or detachable balloons or rotating atherectomy devices, catheters with laser heads and hollow catheters through which radio-opaque, biocompatible substances such as silicon beads, lavalon and gel foam can be injected, are used. The procedures widely used are as follows:

Dilatation of narrowed arteries: Percutaneous transluminal coronary angioplasty (PTCA) refers to dilatation of atheromatous coronary vessels. Renal arteries and carotids can also be dilated, usually with inflatable balloons.

Occlusion of aberrant vessels: The arterial feeder to an arteriovenous malformation or the site of an arteriovenous fistula may be occluded using detachable balloons or injected material.

KEY CONCEPTS

- The *routine* (i.e, in the absence of symptoms or signs) chest and skull X-rays are not cost-effective investigations.
- *Computed tomography (CT)* is an imaging technique which uses a series of collimated X-ray beams passing at different angles through the region of interest followed by measurement of their attenuation by various tissues; a computer then generates a two-dimensional picture of the region imaged based upon the 'X-ray absorption of each point' (pixel) in the tissue slice.
- In *digital subtraction angiography (DSA)*, sequential images are obtained after a rapid intra-vascular injection of radio-contrast. The images are digitised, displayed on a video terminal and then stored on a magnetic tape.
- *Ultrasonography* generates grey scale pictures using sound waves (generated by a piezo-electric crystal) which are reflected between tissues of varying acoustic impedance.
- *Magnetic resonance imaging (MRI)* uses a magnetic field to align protons in tissues within the field of imaging. A radiofrequency pulse is then used to 'flip' them into a high energy state; energy released when the pulse is turned 'off' yields information regarding the chemical constitution of tissues within the imaging field. The 3 dimensional anatomic image can then be reconstructed using a computer.
- *Radionuclides* are substances which (when given orally or parenterally) emit gamma rays that can be detected, quantitated, and localised with a gamma camera.
- A *positron emission tomographic (PET)* scan uses cyclotron-produced radionuclides with very short half-lives to provide three-dimensional sections of organs. This technique permits in situ evaluation of regional tissue metabolism and blood flow.

8

Infectious Diseases

8.1 Principles of infectious diseases

The epidemiology of infections is the systematic study of the determinants of health and infectious diseases in defined populations. Among the first principles of epidemiology of infections is the concept that, at any one time and place, the pattern of infections in the community reflects the complex interactions of the *agent* (the microbe), the *host* (the population), the previous and present *environment,* and the life-style of the community. An agent is an organism capable of causing infection and disease. Several characteristics of an agent affect its ability to cause disease. The *infectivity* of an agent is the ability of an agent to colonise or survive within the body of the host. The *pathogenicity* of an agent is the ability of the agent to damage host tissue and cause disease by its presence or by the production of toxic products; the extent of an agent's pathogenicity describes its *virulence.* The time necessary for an agent to multiply and develop infectivity (for example, in an arthropod) is termed its *extrinsic incubation period.* The facility with which an agent is transmitted characterises its *communicability.* A source of infection is any animate subject or inanimate object which is capable of harbouring the agent. A non-human source or carrier of an agent is called a *vector.* A *reservoir* describes human or non-human vehicles for perpetuating the agent. The term *host* describes any human or non-human species susceptible to colonisation or disease caused by the agent. The interval from the entry of the agent into the host body up to the onset of clinically recognised disease is called the *intrinsic incubation period.* The *period of infectivity* is the interval of time (asymptomatic, symptomatic or convalescent) during which the host is capable of transmitting the agent to another host. Some diseases are most infectious during the incubation period or during the early symptomatic period (as in measles or influenza). Such illnesses are particularly difficult to control as the host goes about his routine, unaware of his infective potential, thereby exposing many persons to the disease. Diseases with long incubation periods are more difficult to control as compared to those with a short incubation period because of the dormant nature of the diseases; the host travels and acts as a carrier for a longer duration. The *attack rate* is the number of persons infected with a specific agent per 1000 people at risk in a defined population. The *case-fatality* rate is the number of deaths per 100 people with the disease. When a disease is constantly present in a defined population at a well defined rate, it is said to be *endemic* in that population. An *epidemic* is defined as the presence of multiple infections and illness from a single or continuing source at a level which exceeds that expected for the defined population (that is, above the endemic level or usual frequency). When a disease is present at a constant high rate in an area, it is said to be *hyperendemic* in that locality. The *temporal* (time course) and *numeric* (numbers) features of an infection depend on the *relative proportions* and *probability of contact* of infected hosts and the susceptible

population. The transmission of infectious diseases within hospitals is termed the *nosocomial spread* of infections.

Biology of Infections and Host Defence Mechanisms

The onset of any infective process begins with the access of the agent to the body of the host. The modes of transmission and the portals of entry vary and knowledge of this is critical for the control of infections. If transmission of the disease is favoured by air (as in streptococci), the epidemiologist must know the conditions favouring the multiplication and spread of the agent (such as overcrowding in the low socioeconomic status groups). Similarly, if human habits influence the transmission of an agent, as in the acquired immunodeficiency disease or *kuru* disease, it is not possible to attempt disease control without attention to the social, psychological and even anthropological details.

Host defence mechanisms determine whether the agent gains access to the host body. The *intact skin* is the first barrier that virtually prevents the entry of any microbe, unless it is breached.[1] Most mucosal surfaces are bathed in secretions containing *lysozyme* which inhibits gram-positive organisms by splitting the muramic acid–*β-(1,4)-N-acetylglucosamine linkage* in the bacterial cell walls. The defence mechanisms of the *respiratory tract* include the nasal filters, mucociliary elevators of the tracheobronchial tree, the cough reflex and the alveolar macrophages; those of the *gastrointestinal tract* include the acid pH of the stomach, the antibacterial properties of the intestinal and pancreaticobiliary enzymes, peristalsis, lymphoid follicles of the gut and the normal indigenous flora. The *genitourinary tract* is protected by its length in men and by the acid pH of the vagina in women; the hypertonicity of the renal medulla and the flushing action of the bladder are other important defence mechanisms.

Once the agent does gain access to the host body, it adheres to the surface and then penetrates local tissues and may eventually disseminate to distant sites either through the bloodstream or by the lymphatic system. Some organisms adhere by way of *fibrillae* (for example, *Streptococci*), while other bacteria express adhesive organelles called *fimbriae* or *pili* (most members of the *Enterobacteriaceae* family). Some organisms cause disease without local invasion by producing extracellular *toxins* (for example, *Vibrio cholerae*); others are armed with enzymes (such as proteases, hyaluronidase) whose activity facilitates local spread. The presence of microorganisms in the host tissue initially elicits an acute inflammatory reaction mediated by *cytokines* (interleukin-1, interferon-γ and the tumour necrosis factor) produced by macrophages and activated lymphocytes. This acute response is not antigen-specific; it is a prelude to a more specific response and is characterised by an increased vascular supply and an enhanced vascular permeability that allows the influx of chemotactic peptides, polymorphonuclear cells and monocytes into the extracellular tissues. Drawn to the organisms by a chemotactic gradient, the phagocytes engulf the organism. This is followed by the development of an *oxidative burst* within the phagocyte and the fusion of the *phagosome* containing the organism with the lysosomes, resulting in the death of the organism. Some organisms (like *Legionella*) do not elicit the oxidative burst response and thereby escape destruction, whereas others produce enzymes (catalase, superoxide dismutase) that destroy the reactive free oxygen radicals generated by the burst. Phagocytosis is facilitated by the presence of *opsonins* (antibody and complement products[2]) on the surface of the organisms. Opsonisation is important for the destruction of capsulated pathogens. Some capsulated

[1] An exception is the human papilloma virus, the causative agent of warts, which can invade intact skin.

[2] For a detailed discussion, see Chapter 17.

organisms (pneumococci, meningococci) have antiphagocytic capsules that prevent opsonic antibodies from binding. The complement system can be activated on the surface of some microorganisms (by the *alternate pathway*) but is usually activated by the *classical pathway* that required presence of immunoglobulins. The complement system lyses the cell wall of the bacterial pathogens and this results in their destruction. Certain strains of bacteria are virulent by virtue of being resistant to serum components (strains of *Neisseria gonorrhoeae* causing disseminated infection). Most *extracellular* bacteria (for example, capsulated bacteria) need only to be phagocytosed to be digested. Some *intracellular* microorganisms (such as *Mycobacteria* or *Salmonella*) are readily ingested but require the activation of macrophages for digestion.

After exposure to a pathogen, both the humoral and cell-mediated immune reponses are triggered. Immunoglobulin M (IgM) is the first antibody formed after exposure to a new antigen (*primary immunisation*). It exists in a monomeric or a pentameric form and serves as a powerful agglutinator of bacteria due to its ability to promptly activate complement. IgG is the major antibody produced after reimmunisation (*memory response* or *secondary immunisation*). It is the most prevalent of all antibody types and is the only one that crosses the placenta, thereby mediating a transplacental transfer of immunity from the mother to the fetus. The newborn baby is consequently immune to several bacterial pathogens until the levels of maternally-acquired antibodies decline. IgA mediates mucosal immunity and IgE has a beneficial role against parasites. IgD is not known to have biological activity. The cellular immune response is mediated by the T lymphocytes. The T cells learn the concept of *self–non-self* in the thymus, where autoreactive clones are removed. The T lymphocytes are activated by any microbial pathogen that they recognise as foreign and the T cytotoxic cells destroy the pathogens with the help of the macrophages which are activated by the T cells.

There are three possible outcomes of this host-agent combat: 1) the microorganism overwhelms the host defences resulting in the death of the host; 2) a state of equilibrium is reached resulting in chronic infection of the host with the agent, or 3) host defences eradicate the agent and a state of health is restored, often but not always with specific protective immunity against the agent.

Body Response to Infections: Some Definitions

Bacteremia is a term used for describing the presence of viable bacteria in blood. When non-bacterial pathogens are present in blood, appropriate terms (such as *fungemia, viremia, parasitemia*) should be used. The term *septicemia* has been used in the past to refer to the presence of microorganisms or their toxins in blood. It has recently been suggested that this term be discarded. *Sepsis* is the term used to refer to the systemic response to infections. Infections often elicit a systemic inflammatory response that is not unique to pathogens but also occurs in other states such as trauma, pancreatitis, ischemia or hemorrhage. The term *systemic inflammatory response syndrome* (SIRS) has been proposed to describe such an inflammatory response. SIRS is characterised by two or more of the following features: 1) body temperature >38°C or <36°C; 2) heart rate >90/min; 3) tachypnea (respiratory rate >20/min) or hyperventilation ($PaCO_2$ <32mmHg); 4) alteration in white blood cell count (>12,000/mm^3, or <4000/mm^3, or >10 per cent immature neutrophils: *band forms*). When SIRS can be attributed to infection, the term sepsis may be used. Sepsis includes a continuum of clinical manifestations. Hence, the term *severe sepsis* has been used to describe sepsis when it is associated with organ dysfunction, hypoperfusion (manifesting as oliguria, lactic acidosis, or altered mental status)

or hypotension. The term *sepsis-induced hypotension* is defined by the presence of a systolic blood pressure <90 mmHg or its reduction by 40 mmHg or more from baseline as a result of an infectious process. *Septic shock* is a subset of sepsis-induced hypotension which persists despite adequate fluid resuscitation, along with the presence of hypoperfusion or organ dysfunction. The term *multiple organ dysfunction syndrome* (MODS) is used to refer to the presence of altered organ function in a patient so acutely ill that homeostasis cannot be maintained without intervention. MODS describes a continuum of manifestations that may or may not be the result of infections (like SIRS). These standardised definitions have been proposed to facilitate clinical trials evaluating treatment regimens for infections complicated by varying degrees of inflammation and organ dysfunction.

KEY CONCEPTS

- The occurrence of illness in humans is the result of the complex interactions between the responsible *agent* (exposure), the *host* and the *environment* (the *epidemiologic triad*).
- The *virulence* of an organism depends on its *infectivity* (ability to colonise) and its *pathogenicity* (ability to damage).
- Diseases which are associated with a long incubation period are more difficult to control.
- The first lines of host defence against microorganisms are the physical and chemical barriers; these include the skin, mucosa, normal secretions, internal sphincters, and the resident endogenous flora.
- Initially, microorganisms elicit a *non-specific* inflammatory host response; the recruitment of polymorphonuclear cells and the elaboration of cytokines are important components of this response. The macrophages of the reticuloendothelial system (splenic and alveolar macrophages, hepatic Kupffer cells, renal mesangial cells and CNS microglia) play an important role in this response.
- An *organism-specific* immune response is also mounted by the host; activation of T and B lymphocytes culminates in immunoglobulin production and complement activation. Cell-mediated immunity plays a critical role in combating intracellular bacteria.
- *Bacteremia* refers to the presence of viable bacteria in blood. *Infection* refers to the presence of a micro-organism in the body with a local inflammatory response. *Sepsis* refers to the presence of a micro-organism in the body with a *systemic* inflammatory response. *Severe sepsis* refers to sepsis associated with organ dysfunction, perfusion abnormalities or hypotension.

8.2 Approach to a patient with infectious disease

Pathophysiology of fever Fever is a term used to refer to an elevation of body temperature above the normal.[1] Fever may be related to an altered set point of the hypothalamic thermostat mechanism due to excessive heat production (as in hyperthyroidism, salicylate poisoning, malignant hyperthermia) or due to reduced heat loss (heatstroke, *datura* poisoning, ectodermal dysplasia). Fever due to infectious diseases is usually due to the first mechanism.

Infective agents (also called *exogenous pyrogens*) are engulfed by phagocytic leucocytes in the tissues. The inflammatory response triggered by the exogenous agent leads to the production of compounds grouped together as *leukotrienes* that help the leucocytes, monocytes and macrophages to engulf the infective agent. Activated phagocytic cells produce several polypeptide compounds, such as interleukin-1, cachectin (also called tumour necrosis factor), interleukin-6 and interferon-α. These compounds are examples of *endogenous pyrogens*. Interleukin-1 acts on the arachidonic acid pathway, stimulating the production of prostaglandins by the vascular endothelial cells of the hypothalamus. Increased levels of prostaglandins E_2 within the hypothalamus accelerate the 'firing rate' of the 'cold-sensitive' cells in the preoptic anterior hypothalamic nuclei and reduce the activity of the 'warm-sensitive' cells. This results in the shifting of the set point of the hypothalamic thermostat towards a higher temperature setting. The vasomotor centre responds by increasing peripheral vascular tone; cutaneous vasoconstriction decreases heat loss. Shivering thermogenesis may also be initiated. The end result is an elevated body temperature. These mechanisms continue until the temperature of blood bathing the hypothalamic neurons reaches the new set point.

[1] Oral temperature of 37.8°C or rectal temperature of 38.2°C is termed normal.

APPROACH TO A PATIENT WITH PYREXIA OF UNKNOWN ORIGIN

Pyrexia of unknown origin (PUO) has been arbitrarily defined as a temperature in excess of 38.3°C (101°F) for a duration of at least three weeks, which remains undiagnosed after a week of investigation within the hospital. The duration of three weeks is used to define PUO as this would exclude most benign causes of short-duration fevers.

Etiology The causes of PUO are listed in Table 8.1. Briefly, about 40–50 per cent of cases of PUO are due to infections. Neoplastic diseases and immunoinflammatory diseases, each account for about 20 per cent, and about 10–20 per cent remain undiagnosed.

Clinical approach A detailed history and a thorough physical examination are the most important components in the evaluation of a patient with PUO. *Confirmation of the presence of fever* is an important first step. The fever must be documented with actual

Table 8.1 Causes of prolonged fever

1. **Infections**
   - A. Pyogenic infection: pyogenic abscess, cholangitis, pelvic abscess, liver and subphrenic abscess, diverticular abscess, thrombophlebitis
   - B. Vascular infection: infective endocarditis, infected vascular access devices
   - C. Chronic granulomatous infection: tuberculosis, atypical mycobacterial infections, fungal infections
   - D. Other prolonged bacterial and rickettsial illnesses: brucellosis, chronic meningococcemia
2. **Immunoinflammatory diseases**: systemic lupus erythematosus, juvenile rheumatoid arthritis (Still's disease), vasculitis including giant cell arteritis
3. **Neoplasms**: primary (renal, pancreas, hepatic, lung, colon), secondary (hepatic secondaries), lymphoid neoplasms (lymphomas)
4. **Granulomatous conditions (non-infectious)**: sarcoidosis
5. **Metabolic and familial conditions**: Familial Mediterranean fever, Fabry's disease
6. **Drug-induced fever**
7. **Factitious fever**
8. **Undiagnosed fever**

measurement with an accurate thermometer and the patient instructed to maintain a temperature record with 4–6 hourly readings. If no fever is documented but the patient claims to be febrile, the possibility of factitious fever must be considered. Once fever has been documented, its *pattern* must be determined. Although a lot has been written about fever patterns, the pattern by itself is seldom if ever diagnostic of a particular infective agent or disease process. It is also well-known that the same agent may produce more than one type of febrile response. The normal body temperature exhibits a diurnal variation with a peak being observed in the evenings. Most fevers tend to exacerbate this diurnal variation. If the temperature touches normal levels at some time over 24 hours, the fever pattern is termed *intermittent. Remittent* fevers exhibit diurnal variation but do not touch normal levels. Most fevers tend to be remittent. *Sustained* continuous fevers (persistent elevation without normal diurnal variation) are often characteristic of typhoid fever, typhus infection or infective endocarditis. High spiking fevers (also called *hectic*) often suggest bacteremia; cholangitis, urinary tract infection, and pyogenic abscesses are examples. Nevertheless, such a pattern can be seen in miliary tuberculosis and lymphomas. A *relapsing* fever is characterised by days of pyrexia interspersed with afebrile periods. Examples include malaria, borreliosis, rat-bite fever and lymphomas.[1]

Besides the pattern, an enquiry must be made regarding *other clinical features* associated with fever as these may also yield clues regarding the etiology. Chills and rigors occur in malaria and bacteremic illnesses; true chills are associated with the chattering of teeth and rattling of the bed. Viral illnesses can cause a chilly sensation but true chills are rare. Prominent night sweats are typical in tuberculosis, lymphomas, brucellosis, infective endocarditis and pyogenic abscesses.

A detailed enquiry is made regarding the presence of *localising symptoms*. The presence of a prominent cough (pulmonary infection), dysuria (urinary infection), focal weakness (neurologic infection), breathlessness (cardiac disease), altered bowel habits (intestinal disease), toothache (dental infection) are examples of localising symptoms. However, some of these symptoms have poor specificity. Prominent joint pains, joint swelling, mucosal ulceration, skin rash or purpura, dryness of mouth or eyes suggest the possibility of an immunoinflammatory disease. Significant weight loss usually indicates a chronic disease, unless it is recent in onset, when it may suggest

[1] A relapsing type of fever seen with Hodgkin's disease and other lymphomas is called Pel-Ebstein fever.

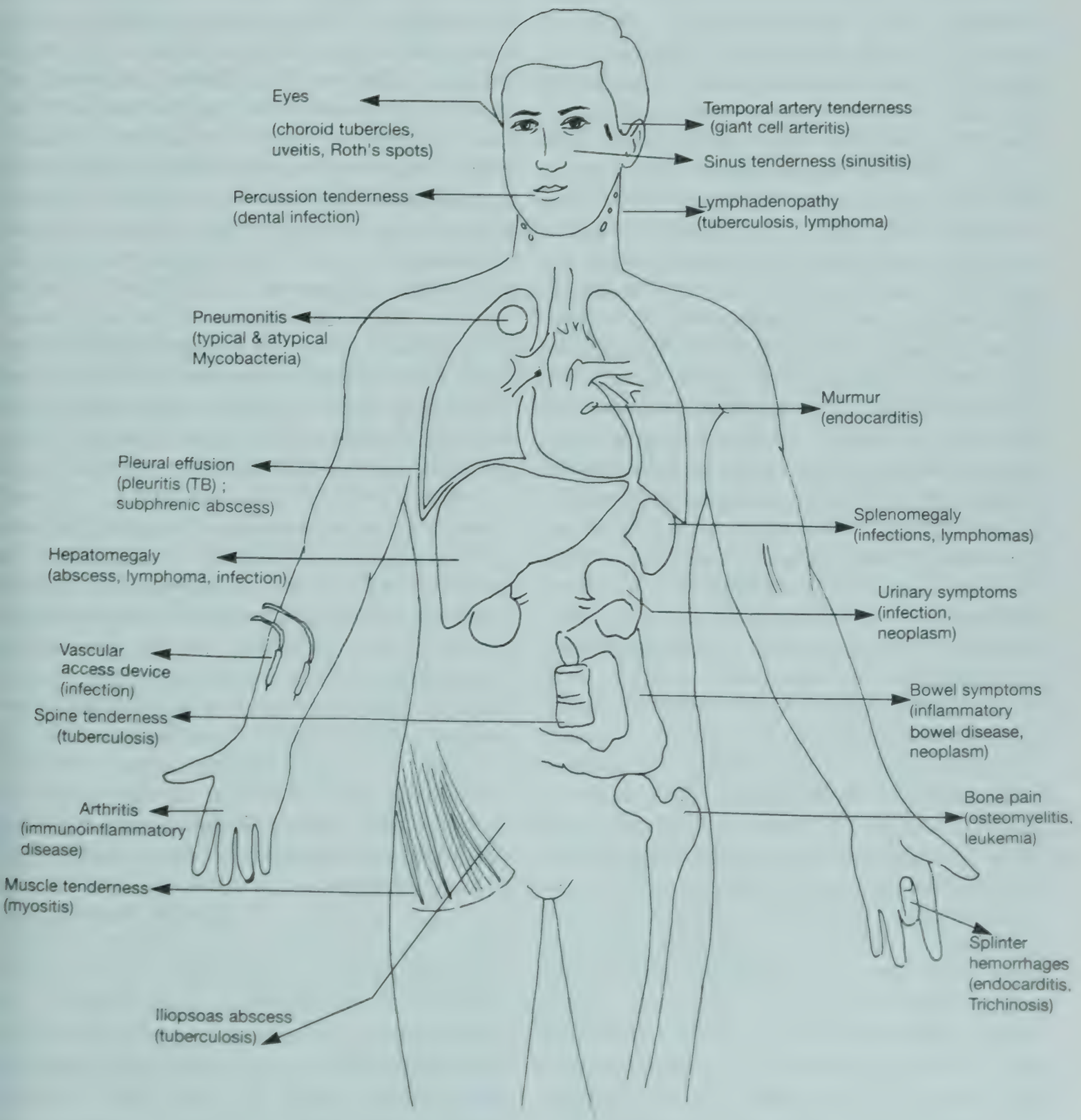


Fig 8.1 Clues to the examination of undiagnosed pyrexia of long duration

an underlying malignancy. Recurrent bleeding, bone pains, or swellings in the neck may point to a lymphoma or lymphoreticular malignancy.

Other important questions include an enquiry into past illnesses (the possibility of recrudescence of tuberculosis), recent surgical procedures (the possibility of localised infection), blood transfusion (blood-borne infections), intravenous drug usage (right-sided endocarditis) and a discrete history of sexual habits (the possibility of a sexually transmitted disease including human immunodeficiency virus [HIV] infection). If drugs are being prescribed for any concomitant chronic conditions, these must be noted in order to exclude the possibility of drug fever. The use of immunosuppressive medication or a history of documented seropositivity for HIV also serve to remind the examiner that infection with an unusual agent may be a possibility. A history of pica in a child may be a clue to the possibility of a parasitic illness (larva migrans, toxoplasmosis). Dietary habits should be ascertained, especially the consumption of raw uncooked food or unpasteurised milk (salmonellosis, brucellosis). A history of travel to an endemic area as well as exposure to pets or livestock is important; cattle rearing has been associated with leptospirosis, toxoplasmosis, salmonellosis, Q fever and, rickettsial disease while bird rearing is associated with psittacosis and cryptococcosis. A visit to a wooded area raises the possibility of tick bites and tick-borne diseases (rickettsial disease). An occupational history is also important for obtaining information regarding exposure to pyrogenic agents such as moulds or fumes. A family history of illness should also be checked as infectious diseases (tuberculosis) and autoimmune diseases may be present in other family members.

The physical examination is often guided by clues in the history but it is important to complement this with a meticulous examination (Fig 8.1). The peripheral pulse rate should be recorded to see if tachycardia is commensurate with the degree of temperature elevation. Bradycardia (relative to that expected from the extent of elevation of temperature) is non-diagnostic; it is encountered on some occasions in typhoid fever, Legionnaire's disease, psittacosis, brucellosis and is quite typical of factitious fever. The presence of pallor is a clue to chronic infection but it is also an important indicator of hematologic disease (especially if severe, and associated with lymphadenopathy or splenomegaly). A careful palpation of lymph nodes is important; the epitrochlear, axillary and supraclavicular lymph nodes should be palpated as these are often ignored. If there is lymph-adenopathy, it must be determined whether it is generalised (suggesting a lymphoma, a viral infection [HIV and infectious mononucleosis being notable], or an immunoinflammatory disease like juvenile rheumatoid arthritis) or localised. If there is localised adenopathy, the area of drainage must be scrutinised (for example, dental infection is associated with anterior cervical adenopathy, inguinal adenopathy is associated with genital disease and supraclavicular lymph node enlargement is associated with cancer of the stomach, breast and lung). Tubercular lymphadenitis (or atypical mycobacterial infection) is an important consideration if there is cervical lymphadenitis. The eyes should be examined carefully: phlycten may be a clue to tuberculosis; conjunctivitis is common in immunoinflammatory disease, leptospirosis, and tularemia. Uveitis is seen in toxoplasmosis, immunoinflammatory diseases, sarcoidosis and inflammatory bowel disease but diagnosis may require a slit-lamp examination. Choroidal tubercles are seen in disseminated tuberculosis. A fundoscopic examination is also important as it may reveal Roth spots (which are a clue to infective endocarditis), or granulomatous changes (as in tuberculosis or sarcoidosis). The oral cavity and teeth must be examined for dental infection (apical abscess masquerading as PUO), and the paranasal sinuses palpated for tenderness (sinusitis).

The temporal artery should also be palpated for eliciting tenderness (in giant cell arteritis). The bones and joints must also be examined with a view to identifying possible immuno-inflammatory disease (arthritis), or infection or neoplastic invasion of the bone marrow (bone tenderness in osteomyelitis, sternal tenderness in hematologic malignancies). The lungs are examined for signs of cavitary disease (tuberculosis) or an effusion (tuberculosis, subdiaphragmatic pathology). When there are signs of a right basal atelectasis along with a right pleural effusion and intercostal tenderness, a liver abscess (usually amebic, occasionally pyogenic) is a possibility. A cardiac murmur in a patient with PUO is an important clue to the possibility of infective endocarditis, provided the murmur is not 'innocent' or 'hemic' (related to associated anemia). Abdominal examination may reveal hepatomegaly, with or without splenomegaly. Hepatomegaly without splenomegaly is seen in liver abscesses and metastatic disease. Splenomegaly without hepatomegaly is seen in infections, lymphomas, hepatic cirrhosis with portal hypertension and endocarditis. Hepatosplenomegaly is a feature of lymphomas, leukemias and chronic infections. The presence of ascites may be indicative of peritoneal seeding with secondaries from an intraabdominal neoplasm or may be due to spontaneous bacterial peritonitis in a known cirrhotic patient. A rectal examination is important and must not be overlooked as it may bring to notice an abscess or a neoplasm. Likewise, a pelvic examination is essential in women with PUO; adnexal tenderness may indicate pelvic inflammatory disease.

Investigations Any patient with PUO should be investigated and a clinical examination performed in an attempt to confirm the diagnosis. The investigations can be organised into a hierarchy of three tiers: basic investigations (the first level), second level procedures and third level procedures.

Basic investigations include a blood count (with differential white cell count), erythrocyte sedimentation rate (ESR), liver function tests, urinalysis, blood and urine cultures, and a chest X-ray. A review of earlier investigations could often unearth valuable information when viewed by a fresh observer. Anemia is a non-specific finding seen in hematologic disorders, chronic infections and in immunoinflammatory diseases. Neutrophilic leucocytosis indicates a bacterial infection, whereas leucopenia is seen in typhoid fever, brucellosis, and systemic lupus erythematosus (SLE). Lymphocytosis with atypical lymphocytes is seen in viral infections (infectious mononucleosis, cytomegalovirus infection, toxoplasmosis). Monocytosis is a feature of tuberculosis, malaria, endocarditis, *kala azar,* brucellosis and some lymphomas. Immature leucocyte forms or pancytopenia may be clues to leukemia. Thrombocytopenia is common in hematologic disorders, spirochaetal infection, infectious mononucleosis, toxoplasmosis, tuberculosis, and SLE. The ESR is usually of little diagnostic value but is an important measure to be used for monitoring disease activity and for assessing response to treatment. Values of ESR that are more than 50 mm/first hour are seen in multiple myeloma, giant cell arteritis, lymphomas, tuberculosis, immunoinflammatory disease (SLE, Still's disease), and infective endocarditis. Liver function tests, although not diagnostic, can reveal evidence of infiltrative, inflammatory or obstructive hepatobiliary disease. Elevated alkaline phosphatase levels indicate infiltrative liver disorders (tuberculosis, lymphomas, metastatic disease). Pyuria may indicate infection (bacterial or tubercular) or immuno-inflammatory disease (sterile pyuria). Blood cultures are likely to be positive in infections associated with bacteremia (endocarditis, pyogenic abscesses). Tests for anti-DNA antibodies can be obtained if SLE is suspected on the basis of clinical evaluation. Serologic tests should be obtained when certain infections are

suspected, such as typhoid and paratyphoid, HIV infection, infectious mononucleosis, syphilis, brucellosis, toxoplasmosis, Q fever, and leptospirosis.

The chest X-ray should be scrutinised with attention to lung fields, hilar lymph nodes, thoracic bones and the cardiac configuration. Whereas apical lesions (especially cavities) raise the possibility of tuberculosis, a normal chest film does not exclude the possibility. Hilar adenopathy is seen in tuberculosis, malignant parenchymal disease (usually unilateral), and in sarcoidosis and lymphomas (usually bilateral). An elevated right hemidiaphragm may suggest an infradiaphragmatic pathology (subphrenic abscess) or a subpulmonic effusion. Bony erosions suggest myeloma or neoplastic infiltration. If bony erosions are seen, a plasma electrophoresis can be obtained to look for the 'M' spike of myelomatoses. An aspiration cytology or a biopsy of palpable lymph glands may be obtained; although granulomatous inflammation is usually indicative of tuberculosis, it should be borne in mind that only the presence of caseation necrosis is diagnostic of tuberculosis. Granulomatous inflammation of lymph nodes may be seen without any caseation necrosis in cat-scratch disease[1] (stellate abscesses surrounded by palisading epitheloid cells), sarcoidosis (giant cells with asteroid bodies, refractile calcium-containing residual bodies and Schaumann bodies [conch-like structures]), and toxoplasmosis (follicular hyperplasia with clusters of epitheloid cells and changes in the germinal centre). Granulomatous inflammation with non-caseating necrosis is also seen in tuberculosis, tularemia and yersinia infections. Lymph node biopsy is also required for diagnosing lymphomas. A bone marrow aspiration or biopsy may be obtained when leukemia, lymphoma or *kala azar* (stained for LD bodies) are suspected.

[1] A rare disease caused by *Bartonella henselae* (main) and *Afipia felis* (occasional) associated with lymphadenopathy and transmitted by the scratch of a dog or cat.

The second level of tests is obtained based on clues regarding the etiology obtained from the first level tests. If these tests are not available at a district level hospital, appropriate referral to a centre with these facilities is necessary. If infective endocarditis is suspected, an echocardiogram should be performed to document vegetations, assess their size and to serve as a baseline. If a hepatic problem such as an abscess is suspected, a hepatic ultrasound and amebic serology may be requisitioned. A needle-aspiration of the abscess may be attempted under sonographic guidance, but may not be required if other investigations support the diagnosis. If an infiltrative hepatic disorder is suspected based on abnormal liver function tests, a needle biopsy (or minilaparotomy for obtaining a wedge of hepatic tissue) of the liver may be attempted after ruling out any coagulation disturbance. If a renal problem is suspected (such as pyonephrosis), a sonographic examination should be obtained, followed by a CT scan if the former is non-contributory. A culture of urine for mycobacteria may be required if renal tuberculosis is a possibility. A biopsy of the temporal arteries may be necessary to substantiate the diagnosis of giant cell arteritis.

If none of the first or second level tests yield clues, third level tests may be ordered. X-rays of the paranasal sinuses and an X-ray of the abdomen and skull can be obtained. These films may help in diagnosing occult sinusitis, paravertebral abscesses or calcified abdominal lymph nodes, and myeloma. An abdominal ultrasound may be considered as it is inexpensive and non-invasive and can screen for biliary tract disease besides detecting abdominal, renal, retroperitoneal or pelvic mass lesions. If sonographic examination is negative, an abdominal CT scan may be ordered if available. The CT scan is very useful for detecting subphrenic, pelvic or intraabdominal abscesses, retroperitoneal lymph nodes, and visceral tumours. Blind biopsy of tissues is generally

non-contributory unless there are clues on clinical examination or other tests to suggest involvement of the particular tissue or organ. The bone marrow is one exception where blind sampling may yield clues. There are anecdotal reports of blind muscle biopsy or biopsy of the temporal artery yielding a diagnosis but there is little justification for undertaking these procedures in the absence of local tenderness.

An exploratory laparotomy was earlier regarded as the last step in investigating PUO when all other tests are negative. It is currently believed that there is little evidence to justify such a major procedure. Instead a therapeutic trial, usually for a presumptive diagnosis of tuberculosis, may be instituted. Such a trial is usually instituted for about six weeks and must include only ethambutol and isoniazid, as streptomycin and rifampicin are effective against other bacteria; a response of the fever is an indication of completing a nine month course after adding the other two drugs. In case there is no response, the antitubercular treatment may be stopped and the patient followed-up. Often a new symptom or sign becomes evident with the passage of time and the diagnosis reveals itself.

Table 8.2 Hospital-acquired infections

Type of infection	*Proportion of all nosocomial infections*	*Diagnosis*	*Common organisms*	*Preventive measures*
Urinary tract infection	40%	$>10^5$ colonies/ml urine	E. coli, Enterococci, Pseudomonas, Klebsiella	avoid indwelling urinary catheters, intermittent catheterisation preferable
Postoperative wound infection	20%	pus discharge at site	Staph. aureus, Staph. epidermidis, Pseudomonas, Enterococci, E. coli, Bacteroides	prophylactic antibiotics for 48 hours in surgery involving 'unclean' areas (e.g. colon), asepsis
Pneumonia	10%	appearance of new pulmonary infiltrate on chest X-ray, sputum production	Pseudomonas, Enterobacter, Klebsiella, E. coli, Acinetobacter, Legionella ; **Viruses** : Respiratory syncytial virus, influenza, Cytomegalovirus	chest physiotherapy, aseptic precautions in patients with tracheostomy or who are on ventilators
Bacteremia	5%	positive blood culture, often patient has a vascular access site	Staph. aureus, Staph. epidermidis, gram-negative bacilli causing urinary tract infection and pneumonia, Candida	change intravenous line once in 72 hours, check for thrombophlebitis
Superinfection of burns	<1%	$>10^6$ bacteria/gram of tissue biopsy	Pseudomonas	meticulous hand washing, prompt removal of urine receptacles; antiseptic fluids may grow Pseudomonas; no 'live' flowers

Table 8.3 Recommended isolation procedures for infectious diseases

Infection	*Separate room*	*Masks*	*Gloves*	*Gowns*	*Hand-washing*
Strict isolation diphtheria, pneumonic plague, chicken pox, disseminated zoster	+	+	+	+	+
Respiratory isolation meningococcal infection, H. influenzae, tuberculosis (sputum positive), pertussis	+ (if possible)	+ (for close contacts if patient is coughing)	–	–	+
Enteric precautions poliomyelitis, shigellosis, salmonella infections, amebic dysentery, cholera, viral hepatitis A	–	–	+ (to handle body secretions)	– (+ if gross soiling present)	+
Contact isolation Methicillin-resistant Staph. aureus, burns	+	+ (if close contact)	+	+	+
Universal blood/body fluid precautions AIDS, hepatitis B positive (recommended for all patients)	–	–	+ (if soiling likely)	+	+

Hospital-acquired Infections

Hospital-acquired infections are infections acquired within the hospital which were neither present nor incubating at the time of hospitalisation. These infections are also referred to as nosocomial infections.[1] The impact of these infections is especially relevant in developing countries with a pressure on utilisation of limited resources. Hospital-acquired infections hinder prompt discharge of patients and substitute the initial problem with at times, a worse one. The most important aspect of nosocomial infection is the knowledge that a majority are preventable provided the hospital staff are aware of their existence and take simple precautions. Most microorganisms within the hospital are spread by *direct* contact (hands of hospital staff or relatives) or *indirect* contact (through droplets). Hand-washing is the simplest and most important procedure for preventing transmission of microorganisms within the hospital. The common nosocomial infections and the guidelines for attending to patients are summarised in Tables 8.2 and 8.3.

[1] Nosocomial, from the Greek word meaning hospital or infirmary

KEY CONCEPTS

- Fever of more than three weeks duration remaining undiagnosed after a week of hospitalisation is defined as pyrexia of unknown origin (PUO).
- PUO may be due to infection, malignancy, inflammatory disease, drugs (drug fever), or factitious. *Infections are the leading causes of PUO* (tuberculosis [often extrapulmonary], HIV infection, infective endocarditis, prolonged mononucleosis, intraabdominal abscess and fungal infections).
- Malignancies associated with PUO are lymphomas, leukemia, renal cell carcinoma, and hepatoma. Immunoinflammatory causes of PUO include SLE and adult Still's disease.
- A proper *detailed history and physical examination is critical* in establishing a diagnosis and for planning investigations. The pattern of fever is seldom diagnostic by itself. Drug history, occupational history and sexual practices are important areas that need to be investigated.
- Routine hematologic and urinary investigations, serum chemistry and chest X-ray are important investigations in all patients. A markedly elevated ESR may indicate an infection or immunoinflammatory disease (temporal arteritis, Still's disease). US/CT may be obtained for evaluating hepatobiliary, renal, retroperitoneal and pelvic sources of PUO and for screening for occult primaries. An echocardiogram may be ordered if endocarditis is suspected. Biopsy of the bone marrow or liver may be useful if the non-invasive investigations do not yield a definitive diagnosis.
- In the absence of a definite diagnosis, a therapeutic trial of antitubercular therapy (INH + ethambutol) may be instituted for six weeks.

8.3 Diagnostic methods in infectious diseases

There are four basic categories of laboratory tests which can be used for the diagnosis of infectious diseases: 1) direct visualisation of the organism, 2) isolation of the organism in culture, 3) immunologic tests based on the detection of microbial antigens or host antibodies, and 4) host 'skin test' responses to injections of attenuated microbial strains.

Microscopic Methods

A *wet mount* is the appropriate technique for the detection of certain motile microbial organisms. A drop of fresh infected specimen (stool, vaginal sample, or exudate) is placed on a slide with a drop of saline, covered with a cover slip and examined. The condenser of the microscope may have to be lowered to provide contrast for organisms such T. pallidum. *A hanging drop* method is used for the identification of Vibrio cholerae (see section 8.5 'Cholera'). Potassium hydroxide is used for fungi in skin scrapings because it dissolves the keratin debris rendering search for the organisms easier. India ink preparations are used to visualise the capsule of cryptococcus (Fig 8.2). Besides simple wet mounts, it may be necessary to stain air-dried, alcohol-fixed or touch preparations of the exudates. A Gram stain is the most common technique. Gram-positive organisms have a lower cell wall lipid content and therefore a decreased permeability to organic solvents as compared to gram-negative microbes (Fig 8.3).[1] Mycobacteria require staining either with the Ziehl-Nielsen technique (Fig 8.4) or with fluorescent auramine-rhodamine. Wright or Giemsa stains demonstrate parasites such as malaria, microfilaria, Borrelia and Babesiosis in a peripheral blood smear. Giemsa stain is also used for demonstrating fungi, trophozoites of Pneumocystis and Toxoplasma, viral inclusions such as in Herpes simplex (Tzanck test). Wright stain is also used to examine conjunctival scrapings for Chlamydia trachomatis. Silver stains (Gomori methenamine, Dieterle) are useful for detecting Pneumocystis, Treponema pallidum, Legionella, Rickettsiae, and certain fungi. Methylene blue is used for identifying fecal leucocytes.

Sometimes a tissue biopsy (or aspirate) is obtained and stained to detect certain microbial pathogens. For instance, skin biopsies are useful for the diagnosis of leprosy, lung biopsy for pneumocystis infection, brain biopsy for herpes simplex encephalitic illness, and liver or bone marrow biopsies for diagnosis of tuberculosis and *kala azar.*

Obtaining specimens and cultures

Blood cultures: Blood cultures are obtained whenever a bacteremic illness is suspected; this includes endocarditis, typhoidal Salmonella infections, brucellosis, pneumococcal pneumonia and septicemia. The recovery of a pathogen is dependent on the number, timing

[1] Gram-positive organisms stain purple from retained crystal violet-iodine complex, whereas gram-negative organisms do not retain this complex and stain red owing to the counterstain.

volume of phlebotomies, the technique used, the handling of the specimen and the method of culture. Usually three blood cultures about 60 minutes apart are sufficient when bacteremia is continuous. If bacteremia is transient and the time of the febrile spike is predictable, blood cultures should be timed about one hour prior to the expected spike.

The venipuncture site is prepared by cleaning an area 2 inches in diameter first with 70% isopropyl alcohol (from the centre to the periphery using a circular motion). The procedure must be repeated with iodine and the site allowed to dry. The femoral vessels are avoided as phlebotomy sites because of the abundance of flora in that region. Sterile gloves are preferable for the venipuncture; if clean but non-sterile gloves are used, the sterilised venipuncture site must not be touched. The tops of the culture bottles are wiped with an alcohol swab, and after venipuncture the blood is inoculated without changing needles.[1] About 20 ml of blood (minimum of 10 ml, preferably 30 ml) should be obtained for each set of cultures; a set of cultures consists of two bottles because the optimum blood/culture medium ratio is 1:9.

When cultures are repeatedly negative, the use of special media for anerobes should be considered. When a skin or mucous membrane commensal (such as Staphylococcus epidermidis) is isolated, repeat cultures are obtained to exclude the possibility of specimen contamination. When repeat cultures yield the same organism, the predictive value of the cultures increases. Prior administration of antibiotics reduces the predictive value of negative cultures.

Cerebrospinal fluid (CSF) culture: Besides examining the CSF for cells and biochemical analysis, CSF should be processed for culture as rapidly as possible. In case a delay is anticipated, the specimen should not be refrigerated as that may kill N. meningitidis. Details of CSF analysis are discussed under infections of the central nervous system.

[1] Changing needles increases the risk of 'needlestick' without decreasing the risk of contamination.

Urine culture: For urine culture, a midstream sample is obtained preferably early in the morning. The patient must be instructed clearly regarding the method of collection: in males the foreskin is retracted and the glans penis cleansed with dilute hexachlorophene solution. In women, the labia are separated and the specimen collected without letting the sterile container touch either the legs or the perineum. The patient is instructed to void the initial 20–30 ml and then, without stopping the urine stream, collect the sample. If a urinary catheter is in place, the urine sample is collected from the specimen port of the catheter (near its junction with the urine bag) after cleaning the site appropriately; the urine should not be obtained from or by puncturing the urine bag. Suprapubic aspiration is an alternative. The urine should be immediately processed or refrigerated as bacteria reproduce readily in urine. More than 1–2 bacteria per 1000 × field on an unspun specimen is associated with colony counts of 10^5/ml or higher (significant bacteriuria). Details of urinalysis are described in the section on urinary tract infections.

Upper respiratory tract secretions: Obtaining a throat swab is important when a group A streptococcal infection, diphtheria, or oropharyngeal gonorrhea is suspected. Under adequate light, a swab is applied firmly over the inflamed area or exudate.

Lower respiratory tract secretions: Expectorated or induced (with inhalation of aerosol mist of 15% saline or 10% glycerol) sputum can be cultured making sure that the specimen does not consist of saliva alone. Specimens containing more than 10 squamous epithelial cells (or fewer than 25 leucocytes) per low power field are unlikely to be lower respiratory tract specimens and can be discarded. Bronchoscopic specimens can be used for culture but there is a potential for contamination while passing the probe through the upper airways. Transtracheal aspiration or percutaneous fluoroscopic-guided

aspiration of pulmonary infiltrates are two other methods of obtaining lung specimens; however, the former is associated with a risk of hemoptysis and the latter with a risk of pneumothorax. These procedures should be undertaken only if the infection is serious enough to justify the risk.

Gastrointestinal secretions: Lower gastrointestinal infections are best evaluated by fresh stool samples. A fresh specimen permits better visualisation of parasitic ova and parasites, and allows the detection of motile pathogens. Upper intestinal pathogens may be better recovered by examining duodenal contents, either by aspirating its contents or using a 'string test' (see giardiasis).

Genital specimens: In men, urethral exudates can be cultured or stained. Massage of the prostate to 'milk' prostatic fluid is appropriate for chronic prostatitis but is contraindicated in acute prostatitis because of the risk of bacteremia. In women with suspected genital infection, an endocervical swab is submitted for culture and the vaginal fluid examined under a light microscope.

Skin and soft tissue specimens: Closed abscesses and soft tissue infections are preferably sampled by aspiration with a sterile syringe. Both aerobic and anerobic cultures are obtained. An applicator swab may also be used.

Sometimes microbial pathogens may have to be cultured from unconventional sites. Occasionally, in pulmonary tuberculosis a gastric aspirate is obtained to search for acid fast bacilli; this has to be done with care as the normal gastric secretions may contain non-pathogenic acid fast mycobacteria. Other sources of microbes that are used for smear and culture include the bone marrow aspirate in typhoid, leishmaniasis, brucellosis, and tuberculosis.

As a general rule, fresh specimens are superior to old ones and multiple specimens preferable to single ones (in terms of microbiologic yield). Generally, bacteria can be cultured on semisolid agar plates or in liquid media. Most body fluids can be transported in sterile containers. If anerobic infection is suspected, then anerobic transport containers (usually carbon dioxide-filled tubes) should be used.

Alternatively, the exudate should be drawn into a sterile syringe, the air expelled, the needle capped and transported immediately to the microbiology laboratory. When viral cultures are being obtained, the samples should be transported immediately or placed in a viral transport medium.[1]

Immunologic Detection of Microbial Antigens or Host Antibodies

Immunologic tests detect either the microbial antigen or measure the host antibody responses. Detection of microbial antigens is more specific as antibody response may indicate present or previous exposure to the pathogen. Microbial antigens are usually detected by precipitin reactions, immunofluorescence assays or radio-/enzyme immunoassays. Thus, counter-immunoelectrophoresis (a type of precipitin reaction) and latex particle agglutination (an agglutination reaction) are used for rapid detection of Streptococcus pneumoniae, H. Influenzae Type b, and Neisseria meningitidis. Agglutination reactions, neutralisation or complement fixation tests are often used for the detection of antibodies. The primary response consists of an IgM response seen within 1–2 weeks of the illness whereas the secondary response consists of IgG production. Serology of this type is complicated in its interpretation and paired samples are often required to demonstrate a rising titre. Serology is commonly used for some bacterial and several viral infections. Fig 8.5 displays the interpretation of paired serum antibody titres. IgM antibodies are diagnostic in toxoplasmosis and hepatitis A. A rising titre of antibodies is used as an adjunct to diagnose typhoid fever and brucellosis

[1] This is an isotonic salt solution containing an antibiotic and a protein.

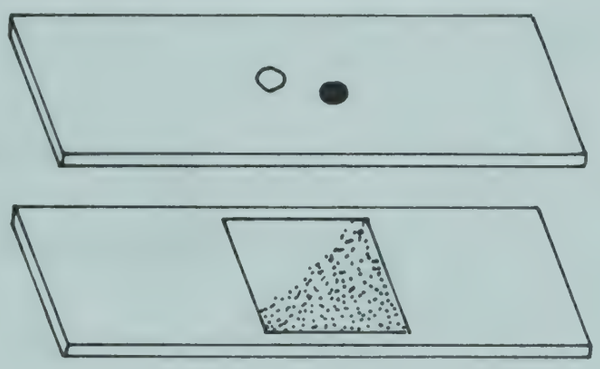
Antibodies are also useful for the diagnosis of syphilis, trypanosomiasis and infectious mononucleosis.

Skin tests evaluate the delayed hypersensitivity response to intradermal injection of attenuated microbial antigens. These tests merely indicate the presence of T cells sensitised to the microbial antigen, that is, they indicate exposure and not disease. They have been used in tuberculosis (Mantoux test), leishmaniasis and histoplasmosis.

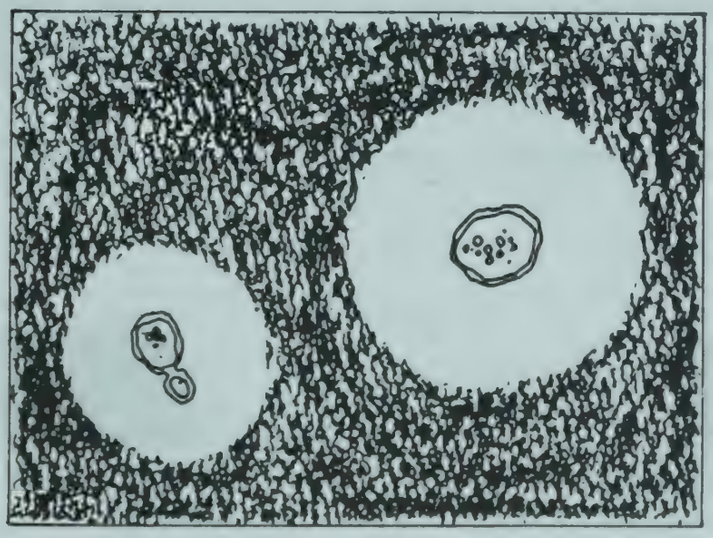
Interpreting in vitro Susceptibility Results

The physician often utilises in vitro susceptibility tests to guide the choice of antibiotics.

However, it should be borne in mind that in vivo and in vitro susceptibilities of microbes may not always be equivalent. An awareness of prior known susceptibilities of organisms in a particular clinical setting (such as a hospital) is as important as the results from the microbiology laboratory.



A. Place loopful of specimen on slide and place loopful of India ink nearby. B. Drop coverslip over 2 loopfuls and examine under high magnification.

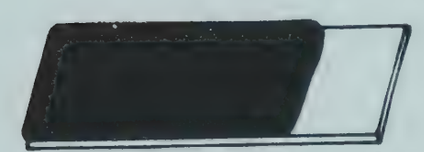


Microscopic view of India ink preparation. (X1,000)

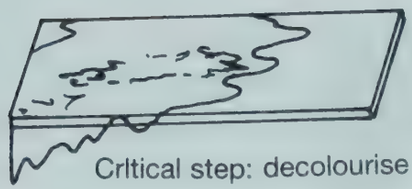
Fig 8.2 India ink preparation

Prepare thin smear. Air-dry and heat- fix.

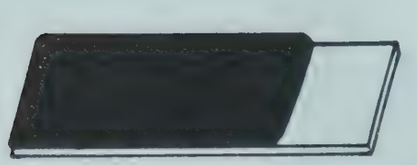
Flood with crystal violet 10 seconds. Rinse with tap water.



Flood with Gram's iodine 10 seconds. Rinse.



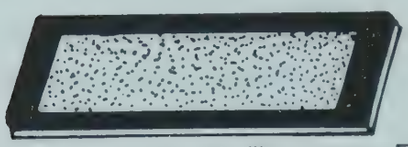
Crltical step: decolourise and rinse



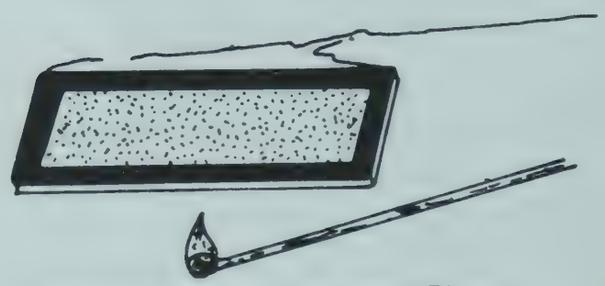
Flood with safranin counterstain 10 seconds. Blot or air-dry.

Fig 8.3 Gram-stain method

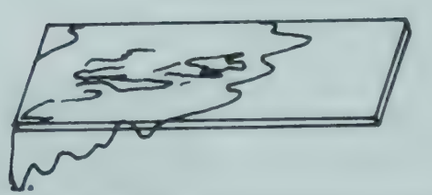
Prepare thin smear. Air-dry and heat-fix.



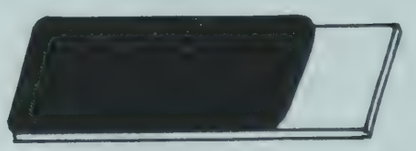
Cover smear with filter paper. Flood with carbol-fuchsin



Steam 3-5 minutes. Let stand. Rinse.

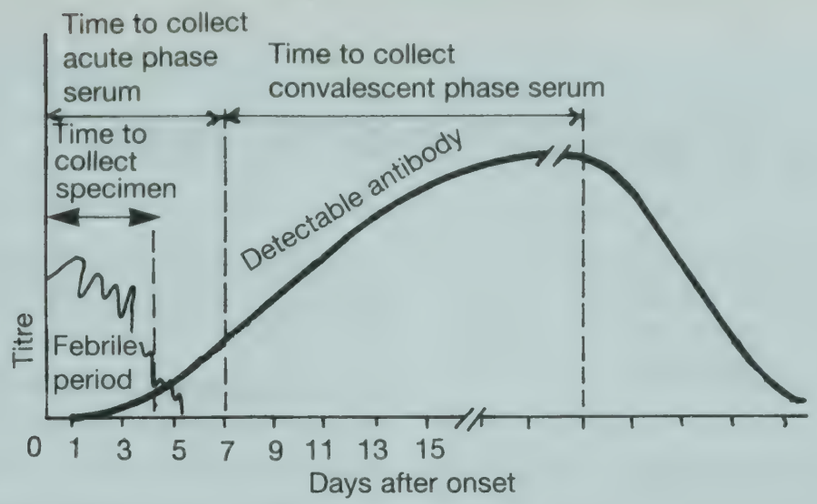


Decolourise with acid alcohol until washing is clear.



Counterstain 20 seconds with methylene blue. Rinse. Air-dry.

Fig 8.4 Ziehl-Nielsen acid-fast stain



Acute titre	*Convalescent titre*	*Interpretation*
less than 1:8	less than 1:8	Negative, no virus disease
less than 1:8	1:32	Significant result, a third specimen should be obtained
1:32	1:32	A chronic presence of a virus or a late case of a viral infection that has a slow titre fall
1:16	1:32	The specimens were probably taken too close together—a third specimen is needed
1:16	1:256	This result is diagnostic for a current infection
1:256	1:256	The peak antibody rise was already reached with the acute phase serum
1:512	1:32	This significant fall would also indicate a recent infection
1:32	1:512	Possible secondary response

Fig 8.5 Natural course of a 'typical' viral infection, illustrating optimal time for collecting specimens for isolation and for serologic studies

KEY CONCEPTS

- Microbiologic confirmation of an infectious disease may be obtained by direct demonstration of the organism, by growing the organism in culture or by serologic methods.
- *Direct demonstration* of an infective agent may be:
  - by *direct microscopy*: India Ink preparation (cryptococci), dark ground illumination (vibrio, spirochetes), KOH preparation (dermatophytes) and wet mount (stool parasites)
  - by *staining*: Gram stain, Leishman stain (malaria), Giemsa stain (chlamydia), Ziehl-Nielsen stain (acid-fast bacilli), silver stains (Pneumocystis)
  - by *antigen detection* using latex agglutination tests (meningococcus, pneumococcus) and enzyme immunoassay
- *Culture methods*: Proper collection technique (for clinical specimen), suitable *transport* and *culture media*, and optimal *growth conditions* may be required for fastidious organisms (such as anerobes). Phenotypic characterisation may be done and antibiotic sensitivity determined after culture of the organism.
- *Serologic methods*: This may be the only method for diagnosing viral, rickettsial, chlamydial and mycoplasma infections. Serology also provides supportive evidence for certain bacterial infections (ASLO for streptococci, Widal for typhoid).

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8.4 Principles of antimicrobial therapy

ANTIBACTERIAL AGENTS

β-Lactam Antibiotics

Penicillins

Penicillins are derivatives of 6-*aminopenicillanic acid* that have a thiazolidine ring connected to a four-member beta-lactam ring[1] which is essential for their action. They inhibit bacterial cell wall synthesis by inhibiting the final step of *trans-peptidation* in the synthesis of the peptidoglycan polymers (Fig 8.6). The loss of cell wall material leads to osmotically-mediated lysis of the cell membranes and cell death. The penicillins are, therefore, bactericidal.

Classification and antimicrobial spectrum

Penicillin G is the prototype compound that still remains highly active against several bacteria like group A and B streptococci, meningococci, pneumococci, gonococci and many anerobes, despite being in extensive clinical use for over forty years. It remains the drug of choice for the treatment of streptococcal sore throat, pneumococcal pneumonia, endocarditis due to viridans streptococci, meningococcal infections, syphilis and infections due to Clostridium perfringens. Several organisms such as most staphylococci, most gram-negative bacilli,

[1] A beta-lactam ring has an amide linkage that joins a carbonyl group and a nitrogen.

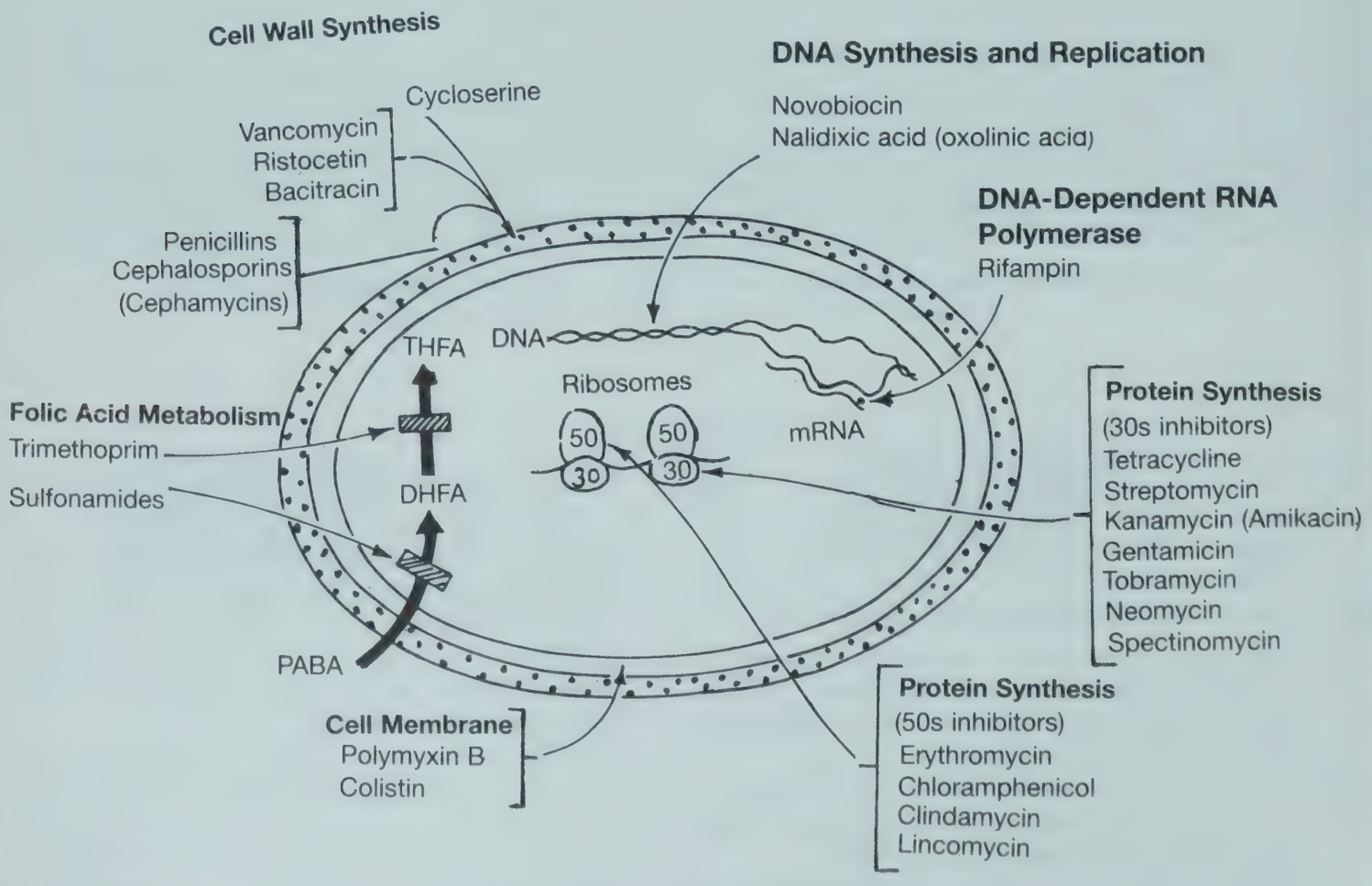

Fig 8.6 Sites of action of various antimicrobial agents.

several species of gonococci and Bacteroides are resistant to Penicillin G by virtue of producing the enzyme beta-lactamase. Congeners of Penicillin G include Penicillin V[2] (which is more stable in the acid environment of the stomach) and the long-acting forms (also called *repository preparations*) procaine penicillin and benzathine penicillin, which are administered by the intramuscular route.

Penicillinase-resistant penicillins include cloxacillin, dicloxacillin, nafcillin and oxacillin. The major indication for these drugs is infections due to beta-lactamase producing Staphylococcus aureus. They are slightly less active than Penicillin G against other species and are ineffective against enterococci.

Aminopenicillins (or semisynthetic penicillins) include ampicillin, amoxycillin and becampicillin. These agents have a similar spectrum of antibacterial action as Penicillin G, with the important difference that they are more effective against certain gram-negative organisms like Salmonella, Shigella, E. coli and Proteus mirabilis. *Anti-pseudomonal penicillins* (or broad-spectrum penicillins) include carbenicillin, ticarcillin and the newer group of *ureidopenicillins* (azlocillin, mezlocillin and piperacillin). These agents are active against Pseudomonas aeruginosa, indole-positive Proteus, and Klebsiella species. They are also moderately effective against anerobes like Bacteroides fragilis. Ticarcillin is more effective against Pseudomonas whereas carbenicillin is more effective against Proteus species. Azlocillin and piperacillin are more effective against Pseudomonas than ticarcillin, and mezlocillin and piperacillin are more effective than carbenicillin against Klebsiella species. All the ureidopenicillins are more effective against Enterobacteriaceae than ticarcillin and carbenicillin.

Pharmacology and dosage Most of the absorbed penicillin is excreted by the kidneys, mainly by tubular secretion (80%) and, to a lesser extent, by glomerular secretion (20%). Aqueous penicillin G is used in a daily dose of 0.6–4 million units administered every 4–6 hours for pneumonia and other infections that are not life-threatening. Severe life-threatening infections (endocarditis or meningitis) require a higher dose of 10–20 million units given intravenously every 4 hours. Penicillin V is indicated for minor pharyngeal or skin infections at a dose of 1–2 grams divided in four daily doses. Procaine penicillin is used in a dose of 0.6 million units administered twice daily by the intramuscular route. Benzathine penicillin is used for the treatment of group A β-hemolytic streptococcal pharyngitis (single intramuscular injection of 1.2 million units), prophylaxis of rheumatic fever (1.2 million units for three weeks), and for the treatment of syphilis (2.4 million units intramuscularly weekly for 1–3 weeks depending on the stage of the disease).

Adverse effects All penicillins can cause allergic reactions. Penicilloic acid and other products of alkaline hydrolysis (*minor antigenic determinants*) are the sensitising antigens that can bind to a host protein and trigger an anaphylactic reaction (0.05%), a serum sickness type of response or a hypersensitivity reaction (1–5%) characterised by skin rash, oral lesions, eosinophilia and interstitial nephritis. Ampicillin is notorious for causing an allergic maculopapular rash and a *non-allergic* rash. The latter occurs typically 3–4 days after initiating therapy and is more common in patients with infectious mononucleosis. Penicillin G can cause severe thrombophlebitis and local pain when used intravenously in high concentrations. The possibility of accumulation of the cations in the penicillin preparation must be borne in mind: for instance, potassium penicillin G preparations contain 1.7 mEq of potassium per million units (care in renal failure) and carbenicillin contains 4.7 mEq of sodium per gram (care in heart failure).

[2] Phenoxymethyl penicillin

Cephalosporins

Cephalosporins are derivatives of *7-amino-cephalosporanic acid.* They resemble the penicillins in having a beta-lactam ring, but also have an adjoining six-membered sulphur-containing ring. They are bactericidal by virtue of inhibiting the transpeptidation reaction for bacterial cell wall synthesis.

Cephalosporins are grouped into three generations on the basis of their antibacterial spectrum. Their activity against gram-positive cocci diminishes from the first to the third generation, whereas activity against gram-negative organisms increases. The third-generation cephalosporins also have good penetration into the cerebrospinal fluid; none of the first-generation drugs and only one second-generation agent (cefuroxime) are effective in bacterial meningitis.

Classification, antimicrobial spectrum and doses Cephalothin (0.5–2 g i.v. or i.m. q 4–6 hours) is the prototype of *first-generation* cephalosporins. Its antibacterial spectrum includes most gram-positive bacteria (S. aureus, pneumococci, all streptococci except enterococci, Actinomyces, and most gram-positive anerobes). It is ineffective against most gram-negative species which produce β-lactamases. Two other first-generation cephalosporins, cephapirin and cephradine, are identical to cephalothin in their antibacterial spectrum. Cefazolin (0.5–2 g i.v. or i.m. q 6–8 hours) also has a similar antibacterial spectrum but has the advantage that intramuscular administration causes little, if any, pain and its blood levels are higher. Oral first-generation cephalosporins (Cephalexin 250 mg–1 g q 6 hours) are used to treat urinary tract infections (caused by susceptible gram-negative bacilli), infections of the respiratory tract, skin and soft tissues in penicillin-allergic patients.

Second-generation cephalosporins have an extended activity against gram-negative bacteria. They have lesser activity against gram-positive bacteria and are not active against enterococci or Pseudomonas. Cefoxitin and cefamandole were the prototype agents; five more parenteral agents (cefotetan, cefmetazole, cefonicid, ceforanide, and cefuroxime) and three oral agents (cefaclor, cefprozil, and cefuroxime axetil) have been introduced subsequently. Cefoxitin (1–2 g i.v. or i.m. q 6–8 hours) is active against many cephalothin-resistant strains of E. coli, Klebsiella, Serratia, and Proteus, while retaining most of the activity against gram-positive cocci and gonococci. However, it is not active against H. influenzae and Enterobacter. A major advantage of cefoxitin is its enhanced activity against gram-positive and gram-negative anerobes (making it valuable for the management of abdominal and pelvic infections). Cefamandole (500 mg–2 g i.v. or i.m. q 6–8 hours) has a somewhat different spectrum of activity from cefoxitin. It is ineffective against B. fragilis, many gonococci, and some Serratia strains, but it is more active against Enterobacter and H. influenzae. Cefuroxime (750 mg–1.5 g i.v. or i.m. q 6–8 hours) is more active than cefamandole against H. influenzae and is the only second-generation cephalosporin to be approved for use in meningitis. Cefaclor (0.25–0.5 g q 8 hours) is an oral second-generation agent with enhanced activity against H. influenzae.

Third-generation cephalosporins differ from other cephalosporins in their enhanced ability to resist hydrolysis by the β-lactamase of many gram-negative bacilli (giving them an expanded antibacterial spectrum), and by their ability to achieve therapeutic levels in the cerebrospinal fluid (making them useful in treating meningitis). Unfortunately, these advantages come at an increased cost, and these agents are less active against gram-positive cocci and are inactive against enterococci and methicillin-resistant S. aureus. However, they are active against strains of H. influenzae, gonococci, and most Salmonella species. Cefotaxime (1–2 g i.v. or i.m. q 4–8 hours) is the first member of the

group. It has been effective in a broad range of infections, including meningitis caused by gram-negative bacilli other than Pseudomonas or pneumococci, pneumonia and bacteremia caused by pneumococci and methicillin-sensitive S. aureus. Ceftazidime (1–2 g i.v. or i.m. q 8–12 hours) is the third-generation cephalosporin with the greatest activity against *P. aeruginosa.* Moxalactam (500 mg–2 g i.v. or i.m. q 6–12 hours) has the greatest activity against anerobes, but it is less active than cefotaxime. Ceftriaxone (1–2 g i.v. or i.m. once or twice daily) has the longest half-life of the third-generation cephalosporins. It is superior to cefuroxime for the treatment of bacterial meningitis in children and is now the treatment of choice for gonorrhea and Lyme disease involving the central nervous system. Cefoperazone (500 mg–1.5 g i.v. or i.m. q 6–12 hours) is less active against many enteric gram-negative bacilli than the other third-generation cephalosporins. Its major asset has been its activity against P. aeruginosa. Cefixime (400 mg/day in one or two doses) is the first oral cephalosporin to be classified as a third-generation agent because of its broad activity against gram-negative organisms. It is also used as a single-dose oral agent for the treatment of uncomplicated gonorrhea. In general, the indications for the use of third-generation cephalosporins include infections with gram-negative organisms resistant to other agents (including gram-negative meningitis).

Adverse effects Cephalosporins can cause the same side effects as penicillins. Most patients with a history of penicillin allergy can tolerate cephalosporins, although cross-allergy (6–10%) is wellknown. Local pain after intramuscular injections and thrombophlebitis after intravenous administration are the principal side effects. Cephalosporins are rarely nephrotoxic when given alone, but some (like cephalothin) can potentiate the nephrotoxicity of aminoglycosides. A prolongation of prothrombin time has been associated with various cephalosporins including cephamandole, moxalactam, cefoperazone and cefotetan.

Carbapenems

Carbapenems differ from penicillins and cephalosporins in the type of ring fused with the beta-lactam ring. Imipenem is the prototype agent. It has the widest range of antibacterial activity among all the β-lactam antibiotics. It has widespread activity against most gram-negative rods (including Pseudomonas aeruginosa), gram-positive organisms and anerobes. The dose is 0.5–1 g i.v. every 6 hours. Imipenem is expensive and should be reserved for organisms resistant to other agents. The drug should not be used for meningitis because the CSF penetration of the drug is variable. Adverse effects include nausea, vomiting, diarrhea, reactions at infusion site, skin rash and seizures (in patients with renal insufficiency). Imipenem is sometimes combined with cilastatin, a drug which increases its levels by decreasing its renal degradation.

Monobactams

Monobactams are drugs with a monocyclic β-lactam ring that are resistant to β-lactamases. These agents have a narrow antimicrobial spectrum of activity, being active against gram-negative organisms (including Pseudomonas) but have no activity against gram-positive organisms or anerobes. Aztreonam (1–2 g i.v. q 6–8 hours) is the prototype agent.

β-Lactamase Inhibitors

These drugs are usually combined with β-lactam agents to prevent their inactivation by β-lactamase. These agents have little, if any, intrinsic antibacterial activity. Clavulanic acid is one such agent which is used in combination with amoxycillin (for oral use) and ticarcillin (for parenteral use). Sulbactam is another agent available in fixed combination with ampicillin for intravenous use. These agents inhibit the β-lactamases produced by S. aureus, B. fragilis, most gonococci, E. coli, Klebsiella, and Proteus.

They do not protect against the β-lactamases produced by most Enterobacter, Pseudomonas and Serratia species. Their side effects are similar to those of penicillins. The amoxycillin-clavulanate combination is an alternative for outpatient therapy of sinusitis, otitis, bronchitis and urinary infections.

Aminoglycosides

Aminoglycosides are bactericidal antibiotics that bind to the 30S ribosome and inhibit bacterial protein synthesis. Unlike β-lactam agents, aminoglycosides produce a 'post-antibiotic' effect.[1] Aminoglycosides are active against aerobic gram-negative bacilli and staphylococci but have poor activity against streptococci and anerobes. All aminoglycosides are excreted by the kidneys and have a similar plasma half-life of about 3 hours. These agents have the potential to produce renal and vestibular ototoxicity; patients receiving any aminoglycoside should be checked frequently for vestibular or auditory dysfunction. To prevent toxicity, serum creatinin levels, creatinine clearance, and urine volume should also be closely monitored. Many hospitals can provide serum levels of aminoglycosides such as gentamicin; therapeutic peak serum levels are important determinants of a clinical response to aminoglycosides. Monitoring serum levels is also the best way to avoid potentially toxic peak levels of drugs in patients with decreased renal function. If serum levels cannot be determined, aminoglycoside dosage can be adjusted on the basis of serum creatinine level. Aminoglycosides can also cause neuromuscular blockade, paresthesia and a peripheral neuropathy.

Streptomycin (administered 0.5 g i.m. q 12 hours) is the prototype drug. Its use is restricted principally to three situations: the initial treatment of tuberculosis (as a part of quadruple regimen in short course chemotherapy), the treatment of enterococcal infections in which synergism between a penicillin and an aminoglycoside is desirable, and the treatment of a few uncommon infections, such as bubonic plague, brucellosis and tularemia.

Kanamycin and neomycin should be used only topically, because of their toxicity. Gentamicin is active against P. aeruginosa and other gram-negative bacilli. It penetrates pleural, ascitic, and synovial fluids in the presence of inflammation but penetration into the cerebrospinal fluid is poor; intrathecal administration of gentamicin is necessary if the drug is used for the treatment of gram-negative bacterial meningitis. The daily dosage of gentamicin for a patient with normal renal function is 3–5 mg/kg, divided into equal doses and administered at 8 hour intervals.

Tobramycin is very similar to gentamicin in pharmacology, dosage and nephrotoxic potential. It is more active against P. aeruginosa and is significantly more expensive than gentamicin.

Amikacin (a semisynthetic derivative of kanamycin) has the same spectrum of activity as gentamicin but is less susceptible to bacterial enzymatic inactivation. It is effective against P. aeruginosa and against many gentamicin- and tobramycin-resistant Enterobacteriaceae (particularly Serratia, Proteus species other than P. mirabilis, and Providencia strains); its principal indication is in the treatment of infections caused by gentamicin- or tobramycin-resistant gram-negative bacilli and as the initial agent for treating presumed gram-negative bacteremia in compromised hosts (when a gentamicin-resistant organism is likely). The recommended dosage in adults with normal renal function is 15 mg/kg/day, administered intramuscularly in equally divided doses every 8–12 hours.

Netilmicin, a semisynthetic aminoglycoside, is pharmacologically similar to gentamicin and has a similar antimicrobial spectrum; it is generally used only for organisms resistant to other aminoglycosides. The recommended dosage is 1–2 mg/kg every eight hours.

[1] Persistent suppression of bacterial growth after removal of the agent

Macrolides

Macrolides are a group of compounds which have a macrocyclic lactone ring to which various sugars are attached. These agents are bacteriostatic and bind to the 50S subunit of the bacterial ribosome, thereby inhibiting bacterial protein synthesis. They are excreted mainly in the bile; dose modification is not necessary in renal failure. Erythromycin is the prototype compound and is also the most widely used agent.

Erythromycin is active against most gram-positive bacteria (S. pneumoniae, S. aureus, Corynebacterium diphtheriae), Mycoplasma pneumoniae, Chlamydia trachomatis, and some gram-negative bacilli (including Legionella pneumophila, Campylobacter, and H. pertussis). It is the drug of choice for treating Legionella and Mycoplasma infections; hence, it is the preferred treatment for patients with 'atypical' pneumonia as well as 'community-acquired' pneumonia. It is also effective for treating Campylobacter gastroenteritis, and for the treatment of diphtheria, chlamydial infections, granuloma inguinale and chancroid (administered along with a sulfonamide). In patients who are allergic to penicillins and cephalosporins, erythromycin is an effective alternative for the treatment of streptococcal pharyngitis, bronchitis, and pneumonia, infections of the skin and soft tissues and syphilis. Topical and oral erythromycin has been used for treating acne. Erythromycin is administered orally in a dosage of 0.25–0.5 g four times a day. Gastrointestinal intolerance is the most common side effect. The stearate form of the drug is preferable to the estolate form because the latter has been reported to cause cholestatic hepatitis on occasion. Intravenous preparations of erythromycin (lactobionate or gluceptate salts, 1–4 g daily) are used for the treatment of severe infections, but are associated with severe thrombophlebitis at infusion sites. Newer macrolides include clarithromycin and azithromycin. These agents are considerably more expensive than erythromycin without having a substantial advantage over it. Clarithromycin is highly active against those organisms that are sensitive to erythromycin and also exhibits excellent activity against M. catarrhalis and H. influenzae. The usual adult dosage is 250–500 mg orally administered twice a day. Azithromycin is another agent which is similar to clarithromycin in its antibacterial spectrum. However, tissue levels of azithromycin are very prolonged (average tissue half-life of 68 hours); tissue levels of the drug remain in the therapeutic range from four to seven days after a five-day treatment course. The usual dosage of azithromycin is 500 mg on the first day followed by 250 mg for 4 days.

Vancomycin

Vancomycin is a bactericidal glycopeptide that impairs bacterial cell wall synthesis. Its spectrum of antibacterial activity is narrow and includes staphylococci, streptococci, pneumococci, enterococci, clostridia, corynebacterium species, and some other gram-positive bacteria. It is bacteriostatic but not bactericidal against some strains of enterococci, S. epidermidis, and corynebacteria. Since oral absorption of vancomycin is poor, this route (125–250 mg every six hours) is used only for the treatment of enterocolitis (either staphylococcal enterocolitis or clostridium difficile [antibiotic-associated] pseudomembranous enterocolitis). The intravenous route (0.5 g every six hours or 1 g every 12 hours) is used to treat severe staphylococcal infections (especially methicillin resistant S. aureus infection) or viridans streptococcal or enterococcal endocarditis in penicillin-allergic patients. Vancomycin is also used for prophylaxis against infective endocarditis in patients with valvular heart disease who are allergic to penicillin. It is combined with an aminoglycoside when treating enterococcal endocarditis and with an aminoglycoside or rifampicin when treating prosthetic valve endocarditis due to S. epidermidis. Vancomycin should always be infused slowly

over a period of one hour to prevent histamine-like reactions.[1] The dosage of vancomycin must be reduced in renal failure.

Tetracyclines

Tetracyclines were originally widely used because of their broad spectrum of activity against both gram-positive and gram-negative bacteria. Because these agents are bacteriostatic, their use has declined with the availability of more effective batericidal agents such as the penicillins, cephalosporins, and the fluoroquinolones. Tetracyclines may be short-acting (prototype tetracycline) or long-acting (prototype doxycycline). These drugs are excreted by the kidneys. Tetracyclines are avoided in children below the age of 9 years, pregnant women (because permanent discolouration of teeth may result in the children) and in renal failure.

Tetracycline still remains the drug of choice for the treatment of rickettsial diseases. It is also a useful alternative for treating mycoplasmal pneumonia and chlamydial diseases (psittacosis, trachoma, and lymphogranuloma venereum). It is also sometimes used in the treatment of non-gonococcal urethritis, brucellosis, plague, cholera, granuloma inguinale, Lyme disease and severe cystic acne. Doxycycline is used for chemoprophylaxis of chloroquine-resistant Plasmodium falciparum infection. Demeclocycline is used for treating the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Tetracycline is usually administered orally, 0.25–0.5 g four times daily.

Doxycycline is given as an initial oral dose of 200 mg on the first day, followed by 100 mg every 12 hours. It has the advantage (over other tetracyclines) that its dose need not be altered in renal failure.

[1] A '*red man syndrome*' has been described with rapid infusions and consists of flushing of skin on the neck and shoulder area, malaise and a shock-like state; slow infusion or pretreatment with antihistamines can help avert this reaction.

Chloramphenicol

Chloramphenicol binds to the 50S subunit of the bacterial ribosome thereby inhibiting bacterial protein synthesis. It is bacteriostatic for many gram-positive and gram-negative bacteria but bactericidal for S.pneumoniae and H.influenzae. It also penetrates the CSF adequately. Traditionally, chloramphenicol has been used for treating typhoid fever, non-typhoidal salmonelloses, meningitis caused by H. influenzae (ampicillin-resistant strains), N. meningitidis, or S. pneumoniae (in penicillin-allergic patients) and infections caused by B. fragilis. The use of chloramphenicol has decreased because of the rare occurrence of aplastic anemia and due to the availability of less toxic alternatives. Chloramphenicol may be given orally (30–50 mg/kg daily) or, less frequently, by the intravenous route (2–4 g/day in divided doses). Blood counts should be checked two or three times weekly when chloramphenicol is used for a prolonged duration.

Sulfonamides

Sulfonamides are antimicrobials that block folate synthesis by bacteria, thereby interfering with nucleic acid synthesis. Although sulfonamides were among the first antimicrobials to be used (along with the penicillins), they no longer play a major clinical role. However, because of their efficacy and low cost, individual sulfonamides are still used to treat uncomplicated urinary tract infections caused by E. coli. Sulfonamides are also useful for treating nocardiosis.

The short-acting sulfonamides consist of sulfisoxazole, sulfadiazine, and trisulfapyrimidines. Crystalluria and hematuria have restricted the use of the less soluble sulfadiazine and this drug has been largely replaced by the more soluble sulfisoxazole. After oral administration (loading dose of 2–4 g, followed by 0.5–1 g every 4–6 hours), sulfisoxazole is rapidly excreted in the urine. The intermediate-acting sulfonamide in use is sulfamethoxazole (loading dose of 2 g orally, followed by 1 g every

12 hours); crystalluria is more frequent with this drug than with sulfisoxazole. Topical sulfonamides are also used to treat superficial ocular infections (sulfacetamide to treat trachoma) and burns (topical silver-sulfadiazine cream).

Trimethoprim-Sulfamethoxazole

Cotrimoxazole consists of trimethoprim and sulfamethoxazole[1] in a synergistic combination (1:5 ratio, that is, 80 mg trimethoprim, 400 mg sulfamethoxazole in a single strength tablet). Trimethoprim is a pyrimidine analogue that blocks bacterial folic acid synthesis (like sulfonamides).

This combination is the treatment of choice for Pneumocystis carinii pneumonia and for nocardiosis. It is also sometimes used for treating uncomplicated urinary tract infections caused by organisms other than E. coli (such as, Klebsiella, Enterobacter, Proteus species), systemic infections caused by chloramphenicol- and ampicillin-resistant Salmonella strains, and for treating shigellosis. Cotrimoxazole has also been used intravenously to treat serious infections due to gram-negative bacteria (including meningitis) when other drugs are ineffective. It is useful for prophylaxis of recurrent bacteriuria and urinary tract infections, acute otitis media, exacerbations of chronic bronchitis (due to H. influenzae and S. pneumoniae), pneumocystis pneumonia (in AIDS patients) and traveller's diarrhea.

The dose of trimethoprim-sulfamethoxazole for the treatment of urinary tract infection is two single-strength tablets (or one double-strength tablet) every 12 hours in adults. The intravenous dose is 8 to 10 mg/kg (based on the trimethoprim component) in 2–4 doses every 6–12 hours. For Pneumocystis pneumonia, the dose is 20 mg/kg (trimethoprim component) in equally divided doses every six hours. Unfortunately patients with AIDS (the situation where the drug combination is most likely to be used) have a high incidence of adverse reactions. A reduction in the dosage is necessary if renal function is impaired. Adverse reactions are similar to those of sulfonamides.

[1] Sulfamethoxazole is used because its half-life (10 hours) is close to that of trimethoprim.

Metronidazole

Metronidazole acts by disrupting bacterial DNA and inhibiting microbial nucleic acid synthesis. The drug is bactericidal against almost all anerobic gram-negative bacilli (including B. fragilis), against most Clostridium species, and has an antiparasitic effect against Trichomonas vaginalis, Entameba histolytica and Giardia lamblia.

Metronidazole is one of the choice drugs for treating anerobic infections of the central nervous system, bones and joints, abdominal and pelvic viscera, and endocarditis; it is administered intravenously as a loading dose of 15 mg/kg followed by 7.5 mg/kg every six hours. The oral dose is 7.5 mg/kg every six hours. The side effects of metronidazole include a metallic taste, nausea and a disulfiram-like effect when alcohol is taken concomitantly. Rare side effects include a peripheral neuropathy, and neutropenia.

Quinolones

Fluoroquinolones are broad-spectrum antimicrobials that exercise a potent bactericidal effect by inhibiting the bacterial enzyme DNA gyrase, that is responsible for maintaining the supercoiled helical structure of DNA. Nalidixic acid was the first quinolone to be used clinically. Newer generation agents include norfloxacin and ciprofloxacin.

The quinolones are bactericidal for most enteric (E. coli, Proteus, Klebsiella, Enterobacter, Salmonella, Shigella, and Campylobacter), and non-enteric (N. gonorrheae, N. meningitidis, and H. influenzae) gram-negative bacilli. They have limited activity against anerobes, staphylococci and streptococci. These compounds are well-absorbed

orally, achieve excellent tissue levels (including the CSF in the presence of meningeal inflammation), and are excreted mainly by the kidneys. The quinolones should be avoided in children and in pregnant or nursing women.

Norfloxacin (400 mg twice daily given either one hour before or two hours after eating) is the oral prototype agent. It has been used successfully for treating urinary tract infections, enteric infections caused by Shigella and Salmonella, and in eradicating the chronic typhoid carrier state. Norfloxacin is also one of the drugs of choice for preventing traveller's diarrhea.

Ciprofloxacin has an antibacterial spectrum nearly identical to that of norfloxacin. Its major advantage is the feasibility of intravenous administration. Indications are similar to norfloxacin. The usual oral dosage of ciprofloxacin is 250 mg twice daily and the intravenous dosage is 400 mg every 12 hours (infused over 1 hour).

Ofloxacin (200–400 mg q 12 hours) is similar to ciprofloxacin but appears less effective against P. aeruginosa but more active against chlamydiae.

MISCELLANEOUS ANTIBACTERIAL AGENTS

Nitrofurantoin

Nitrofurantoin is indicated only in the treatment of uncomplicated, mild urinary tract infections. Its spectrum of antibacterial activity includes E. coli, enterococci, and some strains of Klebsiella and Enterobacter. The drug is administered orally in a dose of 50 to 100 mg four times daily and achieves a high concentration in the urine. It should be avoided in the presence of significant renal impairment.

Clindamycin

Clindamycin (oral 0.6–1.2g/day, i.v. 1.8–3.0g/day) is active against S. aureus, aerobic and anerobic streptococci, Bacteroides (including B. fragilis) and C. perfringens and C. tetani. Pseudomembranous colitis can be a complication of clindamycin therapy. Hence, the drug is reserved for infections that cannot be treated satisfactorily by other agents. One such indication has been for the treatment of aspiration pneumonia and lung abscess.

Polymyxin B and Colistimethate

Polymyxin B and colistimethate (polymyxin E) were used initially to treat infections caused by P. aeruginosa. Newer and less toxic agents are used in preference to these agents. Polymyxin B is still used topically in eye or ear drops.

Spectinomycin

Spectinomycin is mainly used for treating urethral and anogenital gonorrhea in patients who are allergic to penicillins and cephalosporins. A single intramuscular injection of 2 g is effective in treating acute gonococcal urethritis, cervicitis, and proctitis; for the arthritis-dermatitis syndrome, a higher dose (2 g given intramuscularly twice a day for three days) is required.

ANTIFUNGAL AGENTS

Antifungal agents include amphotericin B, flucytosine and the azole group of compounds.

Amphotericin B

Amphotericin B is a fungistatic and fungicidal antibiotic that is part of therapeutic regimen for most systemic mycoses. An initial intravenous dose of 0.1–0.2 mg/kg is increased by 0.1 mg/kg daily until 0.8 mg/kg is given every other day. The total dose is usually about 2.5 grams and each dose should not exceed 50 mg.[1] The drug should be infused over a 2–6 hour period. Adverse reactions are mild and include chills, nausea, vomiting and thrombophlebitis (reduced by injecting 300 units heparin into the infusion). Use of aspirin or an antihistamine (given prior

[1] Amphotericin B should be dissolved in 5% dextrose as a dilutent; saline should not be used as it precipitates the drug.

to, after 3 hours and at the end of infusion) or hydrocortisone (25 mg injected into the tubing at the beginning of infusion) can diminish the frequency of these reactions. Renal toxicity is well-known and renal functions should be monitored during the course of therapy. Potentially less toxic liposomal forms of the drug are being currently evaluated.

Flucytosine

Flucytosine is a nucleoside analogue which gets incorporated into the fungal cell wall and inhibits DNA synthesis. It is used as the sole agent for treating chromomycosis. It is used in an oral daily dose of 150 mg/kg divided into 4 doses. Side effects include leucopenia, thrombocytopenia, hepatotoxicity and diarrhea.

Azoles

Ketoconazole is the compound currently used most often, and it has largely replaced miconazole. It is effective against oral and esophageal candidiasis, and mild to moderate systemic mycoses. Since penetration into the CSF is poor, it should not be used for treating fungal meningitis. The dose is 400–800 mg/day for systemic mycoses and 100–200 mg/day for superficial fungal infections. Side effects include nausea, anorexia, vomiting and, rarely, hepatotoxicity. Ketoconazole also causes a dose-related inhibition of steroidogenesis; loss of libido is common and in rare cases adrenal insufficiency has been reported.

Itraconazole and fluconazole are two of the newer azoles. Itraconazole has better activity against Aspergillus and Sporothrix species than ketoconazole and also lacks its endocrine side effects. Fluconazole is a water-soluble compound that has favourable pharmacokinetic properties, that is, a long half-life and high urinary and CSF concentrations. It holds promise as the agent for oral treatment of cryptococcal meningitis usually with amphotericin B.

ANTIVIRAL AGENTS

Antiviral drugs principally block viral entry into the host cell (amantidine) or interfere with viral DNA/RNA and protein synthesis. A majority of the drugs currently available are nucleoside analogues that are phosphorylated intracellularly to their triphosphate derivatives. The nucleoside triphosphate inhibits viral DNA polymerase, thereby interrupting viral proliferation. Table 8.4 summarises the principal antiviral drugs, their indications and their dosage.

Chemoprophylaxis Antimicrobial agents used for prophylaxis of certain infections are listed in Table 8.5.

Table 8.4 Antiviral drugs

Drug	*Indication*	*Mechanism*	*Dose*	*Comments/side effects*
Amantadine	Prophylaxis of Influenza A	blocks virus entry into host cell/'uncoating' of virus	100 mg oral bd	70% efficacy, insomnia, jitteriness, confusion
Rimantidine	Prophylaxis of Influenza A	same as above	200 mg oral bd	side effects as above but less frequent
Idoxuridine	Herpes simplex keratoconjunctivitis	nucleoside analogue	0.5% ointment q 4 hours	local irritation, edema of eyelids
Ribavirin	Respiratory syncytial virus, Influenza A & B, Lassa fever	nucleoside analogue	1.1 g/day by aerosol	anemia, rash
Vidarabine (Ara-A)	Herpes simplex keratoconjunctivitis and encephalitis; varicella zoster in immunosuppressed	nucleoside analogue	3% ointment for eye use; 15 mg/kg i.v. over 12 hours for 10 days	Acyclovir preferred; side effects include tremors, phlebitis
Acyclovir	Herpes simplex (genital)	nucleoside analogue	200 mg/d oral x 10 d or 400 mg tds for 5 days (genital); 12.4 mg/kg i.v. q 8 hours for 10 days	
	Herpes simplex encephalitis		12.4 mg/kg i.v. infused over 1 hour q 8 hours for 10 days	phlebitis, increased creatinine
	Herpes zoster		800 mg oral/day for 7–10 days	must be given within 48 hours of appearance of vesicles, reduces post-herpetic neuralgia; side effects: lethargy, tremors, drowsiness
Ganciclovir	CMV retinitis/colitis	nucleoside analogue	initial: 5 mg/kg (over 1 hour) i.v. q 12 hours x 2-3 weeks; maintenance: 6 mg/kg q day, 5 days a week	leucopenia, thrombocytopenia, fever, raised liver enzymes
Zidovudine (AZT)	HIV	nucleoside analogue	100 mg oral/day or 200 mg q 8 hours	headache, bone marrow suppression: megaloblastic anemia, leucopenia, nausea, vomiting, fatigue, contusion, myositis
Didanosine	HIV infection intolerant to AZT	nucleoside analogue	≥60 kg: 200 mg oral q 12 hours; < 60 kg: 125 mg oral q 12 hours	peripheral neuropathy, pancreatitis
Foscarnet	CMV retinitis intolerant to Ganciclovir	pyrophosphate analogue	60 mg/kg i.v. q 8 hours for 2 weeks followed by once daily injections	headache, nausea, increased creatinine
Interferon	Chronic hepatitis B/C	blocks transcription and translation of viral RNA	5 million u/d sc or i.m. for 4–6 months	flu-like illness, anorexia, diarrhea, dizziness
Podophyllin	Condyloma acuminatum		topical 25% solution, applied and washed after 2–4 hours	local pain, burning

Table 8.5 Chemoprophylaxis of some infections*

Infective agent/condition	*Indication*	*Antimicrobial agent/dose*
Group A Streptococci	prior rheumatic fever/rheumatic heart disease	Benzathine penicillin 1.2 million units q 21 days; penicillin V 250 mg bd; oral sulfadiazine 1 gram/day
Pneumococci	sickle cell anemia	Penicillin V 250 mg bd
Meningococci	contact of patient with meningococcal disease	Rifampicin 600 mg q 12 hours × 4 doses
H. influenzae	contact of patient with severe infection	Rifampicin 20 mg/kg daily × 4 days
Plague	contact of patient with pneumonic form of disease	Tetracycline 0.5 grams daily × 5 days
Traveller's diarrhea	travel through area endemic for enterotoxigenic E. coli	Doxycycline 100 mg/day
Recurrent urinary infection	women with frequent urinary infections	Cotrimoxazole 1 single-strength tablet daily
Chronic bronchitis	recurrent bronchitis	Cotrimoxazole (2 tablets), Ampicillin *(250 mg tds) at the earliest sign of upper respiratory infection, continued* × 2 weeks

* malarial and endocarditis prophylaxis are covered in sections dealing with these infections

KEY CONCEPTS

- The choice of the antimicrobial used for the treatment of an infection is influenced by several factors: the age of the patient, the site of infection, immune status of the patient, efficacy of the drug, the profile of adverse effects, the prevalence of antimicrobial resistance and the concomitant presence of other systemic diseases or organ dysfunction.
- The *cephalosporins* include three generations of agents. The second generation extends the antimicrobial spectrum of the first generation to include a wide range of gram-negative organisms. The third generation is effective against enteric gram-negative rods and Pseudomonas.
- The *β-lactams* act by inhibiting the incorporation of peptidoglycan into the bacterial cell wall. Penicillin G still remains the drug of choice for syphilis, meningococci, clostridia, and pneumococcus. Ampicillin has an extended spectrum of activity against gram-negative rods (Salmonella, Hemophilus influenzae). Penicillinase-resistant penicillins are the drugs of choice for infections due to β-lactamase producing staphylococci. Piperacillin and ticarcillin are antipseudomonal penicillins.
- The *aminoglycosides* act by binding to the 30S ribosomal subunit. They are effective in urinary tract infections, and are used along with penicillins for treating enterococci. Streptomycin is effective against Mycobacterium tuberculosis and is the drug of choice for plague, tularemia and glanders. Aminoglycosides are associated with renal and vestibular ototoxicity.
- The macrolides (erythromycin group) bind to the 50S ribosomal unit. They are the agents of choice for the treatment of Legionella, Mycoplasma and Chlamydia. They are also the agents of choice for combating gram-positive organisms (Streptococci, Staphylococci) in penicillin-allergic patients.
- *Tetracyclines* bind to the 30S ribosomal subunit and are highly effective in brucellosis, rickettsial disease, tularemia, plague and granuloma inguinale. Tetracyclines are avoided in children, pregnancy and renal failure.

- *Chloramphenicol* binds to the 50S ribosomal subunit. Although the potential hematologic toxicity has restricted its use, it is highly effective against Salmonella, Meningococci, Hemophilus influenzae, and rickettsiae.
- The *fluoroquinolones* inhibit DNA topoisomerase. They are highly effective against most gram-negative rods and Pseudomonas. They are effective in traveller's diarrhea, typhoid fever, and urinary and respiratory tract infections. They are avoided in children.
- Cotrimoxazole is effective in typhoid, Pneumocystis pneumonia, and urinary tract infections. Metronidazole is highly effective in amebiasis, trichomoniasis and anerobic infections. Pyrantel pamoate and mebendazole are the agents of choice for most intestinal helminths.
- Antiviral agents include several nucleoside analogues. Amantadine is effective in Influenza A, idoxuridine against herpes simplex, vidarabine against herpes simplex, acyclovir against herpes simplex and zoster, and zidovudine against HIV.

8.5 Bacterial infections

DISEASES DUE TO GRAM-POSITIVE BACTERIA

Streptococcal Infections

Microbiology and the disease spectrum Streptococci are classified into Groups A–H and K–T based on the carbohydrate content of their cell walls. **Group A** β-hemolytic[1] streptococci are the most virulent species for human beings and infections by these organisms will be discussed in detail. **Group B** streptococci include the species *Streptococcus agalactiae* and are important causes of maternal chorioamnionitis, septic abortion, puerperal sepsis and neonatal sepsis. **Group C** streptococci include the species *Streptococcus equisimilis* and can cause pharyngitis, cervical adenitis and disseminated deep tissue infections. **Group D** streptococci include enterococcal (*Enterococcus fecalis*[2]) and non-enterococcal species (*S. bovis*) and cause urinary tract infections, endocarditis, abdominal sepsis and wound infections. *S. bovis* infection is seen in patients with bowel neoplasia or cirrhosis. **Group G** streptococci cause cellulitis and infect decubitus ulcers in subjects with chronic lymphatic obstruction or venous insufficiency.

Group A Streptococcal infections: Streptococcal pharyngitis

Epidemiology Streptococcal pharyngitis affects children in the age group 5–15 years. It accounts for 95 per cent of all cases of bacterial pharyngitis. Overcrowding is an important factor in the spread of streptococci, and person to person spread by droplet infection is the mode of transmission. The peak incidence in India is in the months from October to April. The organism frequently colonises the throats of people who do not develop the disease but serve as carriers for the spread of infection to others.

Clinical features Only 20 per cent of patients with streptococcal pharyngitis have a complete clinical picture of a bacterial sore throat. The majority of sore throats are asymptomatic or mildly so. The classical manifestations include acute onset of high grade fever, headache and throat pain. Physical examination reveals diffuse pharyngeal erythema, enlarged tonsils covered with a whitish exudate and tender cervical and submandibular lymph nodes. Vomiting and abdominal pain are common features in children and convulsions may rarely occur. No symptom or sign is specific for the streptococcal etiology of a sore throat.[3] The presence of prominent cough, laryngitis or rhinorrhea may suggest a non-streptococcal etiology of the sore throat. Diphtheria is diagnosed if a 'pseudomembrane' is present. White patches with only mild erythema in an immunocompromised subject may indicate candidal pharyngitis. The presence of shallow ulcers and severe halitosis[4] may

[1] Beta-hemolysis refers to complete lysis of erythrocytes and results in a clear zone around colonies.

[2] Formerly called streptococcus fecalis

[3] The only sign with a statistical association with serologically confirmed streptococcal pharyngitis is cervical adenitis.

[4] Halitosis refers to the presence of bad breath.

suggest infection due to anerobic fuso-spirochetes (*Vincent's organisms*).

The strains of Streptococcus pyogenes that have a lysogenic phage can produce an *erythrogenic toxin* that causes *scarlet fever*. Scarlet fever usually follows streptococcal pharyngitis but may follow wound infections or puerperal sepsis. Scarlet fever is characterised by a diffuse pink-red cutaneous rash which begins initially on the neck and upper chest, usually within two days of the onset of sore throat. The rash spreads to the abdomen and the rest of the body but spares the palms and soles. It blanches on pressure, imparts a 'sandpaper texture' to the skin, lasts for about 4 days and is followed by desquamation. Associated features of scarlet fever include a *strawberry tongue* (inflamed papillae), and *Pastia's lines* (prominent lines along the skin creases).

Complications The acute suppurative complications of a streptococcal sore throat include otitis media, sinusitis and development of a peritonsillar abscess (quinsy). The delayed non-suppurative complications (more than two weeks after the sore throat) include the risk of developing acute rheumatic fever (0.05–3%) or acute glomerulonephritis (0.2–20%).

Other Group A streptococcal infections

Erysipelas is an acute streptococcal skin infection affecting infants and young children with marked involvement of subcutaneous lymphatic vessels. The affected skin is initially red but soon vesicles and bullae appear. The margins of the lesion are sharply demarcated and elevated; the skin looks like an orange peel. The lesions itch and sting. They heal with crusting and central clearing is typical.

Impetigo is a localised bullous pyogenic infection of the skin affecting children in the hot humid tropics who are in the age group 2–6 years. Overcrowding and poor skin hygiene are the predisposing factors. Scratching spreads the infection. Though *staphylococci* are the commonest cause, occasionally streptococci are implicated in the disorder. Streptococcal impetigo may be complicated by acute glomerulonephritis (but not by acute rheumatic fever).

Streptococci are the commonest cause of bacterial lymphangitis and are also an uncommon cause of bacterial pneumonia. Streptococcal pneumonia resembles a bacterial pneumonia with the difference that there is often an early and rapid accumulation of serosanguinous empyema fluid.

Streptococci can also cause a *necrotising fasciitis* that mimics gas gangrene. Elderly people who have diabetes or a vascular disease and have undergone recent surgery, or who have skin wounds are especially susceptible. Fever, lethargy and disorientation are important systemic features which precede the cutaneous lesions. Red-streaked painful skin lesions are surrounded by darker red inflamed tissues. Bullae with yellow or reddish black fluid develop and rupture. The tissues slough extensively and bacteremia, metastatic abscesses and thrombophlebitis are important complications.

Diagnosis and treatment Acute streptococcal pharyngitis is accompanied by a polymorphonuclear leucocytosis and an elevated sedimentation rate. A specific diagnosis can be established by either culturing the organism from the throat (sensitivity of 70–80%) or by identification of streptococcal antigens in tissue exudates using rapid diagnostic kits (sensitivity of 40%). Indirect evidence of a recent streptococcal infection can be obtained by serial serological estimation of antistreptococcal antibodies. A rise in titres of antibodies[1] confirms recent streptococcal infection. The commonest antibody estimated is antistreptolysin-O (*ASLO*) which rises in about 80 per cent of pharyngeal infections but not after streptococcal skin infections.

Penicillin is the treatment of choice for Group A streptococcal pharyngeal and

[1] A rise by at least 2 tube dilutions is needed

superfical skin infections. A single intramuscular injection of benzathine penicillin at a dose of 50,000 units/kg for children and 1.2 million units for adults is usually sufficient. The injection is, however, painful and hence oral penicillin V (25–50 mg/ kg/ day or 250 mg qid) for 10 days is an attractive alternative. Erythromycin (250 mg qid) is an effective alternative in the penicillin-allergic subject.

Streptococcal fasciitis requires immediate debridement of all necrotic tissues in addition to parenteral penicillin administration.

Group B streptococcal infections

Early-onset infections occur in infants who are less than 5 days old, and are due to organisms acquired from the maternal genital tract. They are characterised by pneumonia, presumably due to aspiration of infected amniotic fluid. *Late-onset* infections are nosocomial in origin and are characterisied by meningitis and bacteremia.

Adult infections Infections in adults due to Group B streptococci are opportunistic and affect patients with diabetes mellitus, malignancies and immunosuppressed states. The infections may affect the urinary tract, lungs, meninges or joints.

All group B streptococcal infections are sensitive to penicillin.

Infections due to Viridans streptococci

Microbiology Viridans streptococci are a group of α-hemolytic organisms[1] that do not have group-specific wall antigens and do not belong to any Lancefield group. Five such species have been identified. These are *salivarius, milleri, mitior, sanguis and mutans.*

Clinical infections Viridans streptococci are the commonest cause of subacute bacterial endocarditis. They are also associated with dental caries. *S. milleri* is the most virulent, and endocarditis associated with it is likely to be complicated by abscesses. Viridans streptococci can occasionally cause liver and brain abscesses, empyema and peritonitis.

Infections due to Enterococci

Microbiology and pathogenesis Enterococci are gram-positive cocci originally classified as group D streptococci, but now reclassified as a separate genus *Enterococcus. E. fecalis* (90%) and *E. faecium* (10%) cause clinical infections. Enterococci produce aggregation substances that help them adhere to renal tubular cells.[2] Enterococci have a class of penicillin-binding proteins that allow synthesis of the cell wall even in the presence of penicillin.

Epidemiology Enterococci are predominantly spread by the nosocomial route and are the second most common cause of nosocomial infections after *Escherichia coli.* Although it was felt initially that most enterococcal infections were endogenous, it is currently believed that enterococci spread from person to person and that personnel are the primary source of enterococcal infections.

Clinical infections Urinary tract infections are the most common enterococcal infections. They are usually acquired either nosocomially or after urethral instrumentation. Infection of pelvic and intraabdominal wounds is the second most common infection due to enterococci. Bacteremia and endocarditis are the third most common category of infections due to enterococci. Rarely, they may cause meningitis, especially in neonates.

Treatment Urinary tract infections can be treated with penicillin or ampicillin provided the infection is with strains that do not produce beta-lactamase. Nitrofurantoin and vancomycin are alternatives. The treatment of beta-lactamase

[1] Alpha hemolysis is the incomplete destruction of erythrocytes resulting in a green colour of the medium surrounding the colonies.

[2] This is mediated via a class of receptors known as *integrins.*

producing organisms or of enterococcal meningitis or endocarditis is best achieved with the use of a combination of penicillin (3 million units q 4 hours) or ampicillin (2 q 6 hours) with an aminoglycoside (gentamicin 1 mg/kg every 8 hours) or vancomycin (1 g q 12 hours).

Staphylococcal Infections

Microbiology Staphylococci are gram-positive cocci that grow in irregular clusters and have cell walls which contain *teichoic acids.* Three species are of medical importance for human beings. *Staphylococcus aureus* produces a golden yellow pigment, causes complete hemolysis of blood agar, is encapsulated, contains *ribitol* teichoic acid, ferments mannitol and produces an extracellular product *coagulase* that can clot plasma. It is responsible for most human staphylococcal infections. *Staphylococcus epidermidis* has white colonies, contains *glycerol* teichoic acid, does not ferment mannitol and only a few strains produce hemolysis on blood agar. *Staphylococcus saprophyticus* has grey-white colonies, is non-hemolytic and can cause cystitis.

Epidemiology Staphylococci are ubiquitous. *Staphylococcus epidermidis* is a normal resident of the skin. About 20 per cent of healthy adults carry *Staphylococcus aureus* on their skin or in the anterior nares. Hospitalised patients have a higher carrier rate and often harbour antibiotic-resistant species. Person to person spread via hands is the most common mode of spread of the organism.

Infections due to Staphylococcus aureus

Superficial skin infections *Staphylococcus aureus* is the commonest cause of *pyoderma.* The term *impetigo contagiosa* is used for the superficial vesiculopustular skin infection that commonly occurs on the legs, arms and face of children. The lesions begin as red maculopapules that soon become yellow vesicles; the vesicles may become bullous (bullous impetigo) and the lesion becomes exudative and crusted in parts. Itching is common and scratching further spreads the infection to the surrounding uninfected skin. Impetigo heals without scar formation. On occasion, the infection penetrates deeper and the lesions appear purulent and ulcerative: *ecthyma.* Ecthyma usually heals with scarring.

Folliculitis is an infection of the hair follicles which typically manifests as a superficial tender pustule or nodule surrounding the hair. Folliculitis may become chronic in areas where the hair follicles are deep in the skin such as in the bearded area of the face (*sycosis barbae*). *Furunculosis* is the development of a *perifollicular* infection, commonly on the skin over the neck, breast or buttocks. Initially a red hot tender nodule is seen which soon becomes a pustule. The pustule discharges its core of necrotic tissue (*pus*). Furuncles often form in clusters and the infection spreads subcutaneously resulting in deep suppuration which discharges through a number of pores. These coalescent furuncles form a *carbuncle.* Carbuncles occur more often in elderly men, most commonly on the nape of the neck. Diabetes mellitus is a common predisposing condition.

Hidradenitis suppurativa is a suppurative infection of the apocrine sweat glands, most often in the axilla and the groin. An infection of the sweat glands results in obstruction and rupture of their ducts. Clinically, there is evidence of subcutaneous inflamed nodules with sinus tract formation.

Treatment with topical mupirocin, applied for 3 to 5 days has been found to be effective for the treatment of impetigo. If there is no response, oral penicillin (cloxacillin 250–500 mg qid for 10 days) is effective in most cases. Erythromycin is an alternative in the penicillin-allergic patient. Folliculitis, furunculosis and carbuncles are treated along similar lines as impetigo. Surgical excision of the infected area may be needed for the treatment of carbuncles and hidradenitis suppurativa.

Toxin-related Staphylococcal skin disease Phage group II strains of *S. aureus* can produce a toxin called *exfoliatin* that can cause three syndromes: 1) In infants and children there is generalised bullous formation with larger areas of red denuded skin: *toxic epidermal necrolysis.*[1] 2) In older children *localised* bullae may form– *Lyell syndrome.* 3) Some children or adults may develop a *scarlatina-like* rash (mimicking scarlet fever).

Staphylococcal pneumonia Staphylococcal pneumonia occurs in subjects with chronic bronchopulmonary disorders, in intubated subjects (as a nosocomial infection) and in children with cystic fibrosis. The clinical features resemble that of bacterial pneumonia but there is a greater chance of abscess formation and empyema. Thin-walled cavities called *pneumatocoeles* may develop, especially in neonates with staphylococcal pneumonia. The treatment of bacterial pneumonias is described in a separate section.

Staphylococcal osteomyelitis This condition occurs principally in children under 12 years of age and there is evidence of a preceding skin infection in about 50 per cent of patients. The vertebral column is the most common site of involvement with a predilection for the lumbar spine. Fever, local pain and tenderness, and leucocytosis are prominent features. Radionuclide bone scans are abnormal early in the course of the disease; radiologic signs of rarefaction of bone or osteolytic lesions accompanied by a periosteal reaction may take 10 to 14 days to become evident. Epidural abscess, spinal cord compression or spillover to periarticular regions (resulting in a septic arthritis) are important complications. The presence of pain in the back accompanied by radicular symptoms or signs should alert the clinician to this possibility. The treatment consists of parenteral antibiotics (see later). Surgery may be needed to remove devitalised bone, drain abscesses and to relieve spinal cord compression. Occasionally, the bone infection may persist as an indolent cavity surrounded by dense granulation tissue: the so-called *Brodie abscess.*

Staphylococcal enterocolitis In hospitalised patients who have undergone recent abdominal surgery or who have received antibiotics for bowel preparation, *Staphylococcus* can cause an enterocolitic illness characterised by fever, ileus, abdominal distension and diarrhea. The disorder must be differentiated from *pseudomembranous enterocolitis* due to toxin-producing *Clostridium difficile.* The simultaneous presence of ileitis and colitis and the presence of fecal leucocytes and staphylococci (in clumps) favours a staphylococcal etiology of the syndrome. Oral vancomycin (250–500 mg q 6 hours) is effective treatment of both conditions.

Staphylococcal food poisoning This is an acute disease caused by the ingestion of enterotoxin producing staphylococci and is characterised by the onset of vomiting and diarrhea approximately 2 to 8 hours after the ingestion of contaminated food. Food handlers with skin infections who handle food which is a good medium for the survival of staphylococci (custard, pastries, milk and meat) are responsible for outbreaks. There is no mucosal ulceration (unlike the enterocolitis described above), the attack is brief (3 to 6 hours) and complete recovery with intravenous hydration is typical.

Toxic shock syndrome (TSS) TSS is a disorder caused by exotoxin producing strains of phage group 1 *Staphylococcus aureus.* The syndrome was initially described as related to the use of contaminated tampons. It is characterised by the onset with menses of a high grade fever, vomiting, diarrhea and a diffuse rash[2] that

[1] Also sometimes called Ritter syndrome or scalded baby syndrome

[2] Typically a sunburn-like erythroderma

desquamates on the palms and soles. The syndrome progresses rapidly to shock if untreated. Renal dysfunction (manifest as azotemia), respiratory dysfunction (adult respiratory distress syndrome), hepatitis and disseminated intravascular coagulation have been known to complicate the illness. Management consists of removal of the foreign body (for example, a tampon), parenteral antibiotics and watching out for and treating complications.

Staphylococcal bacteremia and endocarditis Staphylococci (especially *Staphylococcus epidermidis*) are notorious for colonising intravascular catheters, dialysis access sites and other foreign bodies. From these localised sites, the organisms may disseminate themselves. Intravenous drug addicts and patients with extensive burns are likely candidates for staphylococcal bacteremia (usually due to *S. aureus*). S. aureus is the commonest cause of bacteremia, especially that which is hospital-related. There is a high incidence of complicating endocarditis and development of metastatic abscesses in staphylococcal bacteremias. Persistent high grade fever is common and associated shock may develop. A diagnosis is established by positive blood cultures.

Tropical pyomyositis Tropical pyomyositis is a pyogenic infection of subfascial muscle planes seen in the tropics and is commonly due to *S. aureus*. The disease affects mostly young men and is commonly associated with a history of prior muscular trauma. A history of pyoderma is uncommon. An association with parasitic diseases such as lymphatic filariasis has been described. Usually a lower extremity muscle group is affected, with pain and local tenderness as prominent features. Since the infection is deep seated, the overlying skin may appear normal without any redness or warmth. Fluctuation is usually not elicitable and the affected muscle may feel wooden and swollen, mimicking a muscle tumour. Metastatic abscesses may develop during the course of the disease and fever may be prominent. The diagnosis is readily established by needle aspiration of the affected muscle and culture of the pus obtained. Effective treatment consists of parenteral antibiotic treatment, and local drainage and debridement of the muscle tissues.

Choice of antibiotics in staphylococcal disease
Most community-acquired staphylococci and almost all hospital-acquired strains tend to be resistant to penicillin G, ampicillin and the antipseudomonal penicillins. One of the penicillinase-resistant penicillins is usually the agent of choice (cloxacillin or nafcillin 2 g i.v. every 4 hrs). Cephalosporins and vancomycin are also effective. *Methicillin-resistant Staphylococcus aureus* (MRSA) can be treated with vancomycin (500 mg i.v. 6 hours) or sulfamethoxazole/trimethoprim (50–75 mg/kg/day of sulfamethoxazole and 10–15 mg/kg/ day of trimethoprim). Rifampicin (600 mg/day) and aminoglycosides (gentamicin 1.5 mg/kg every 8 hours) are useful adjuncts in treating MRSA infections and staphylococcal prosthetic valve endocarditis. Isolated bacteremia without endocarditis can be treated for 2 weeks. The presence of endocarditis or osteomyelitis increases the duration of antibiotic administration to 6 weeks. Surgical intervention may be required for endocarditis and its complications.

Infections due to Staphylococcus epidermidis
S. epidermidis is the commonest isolate in nosocomial bacteremias but it is usually a contaminant in this setting. It is a common cause of bacteremia in patients with central venous catheters, dialysis arteriovenous shunts, in neutropenic cancer patients and intravascular prosthetic devices (such as vascular grafts). It is a common cause of meningitis in patients with a central nervous system shunt in place. It is also the commonest cause of prosthetic valve endocarditis. Infections of foreign bodies or implants are particularly difficult to eradicate as

S. epidermidis adheres firmly to the foreign body and covers itself with a layer or protective *glycocalyx.*

Infection must be distinguished from contamination by repeating the blood cultures and with the culture of the removed device. Strains of hospital *S. epidermidis* isolated in the hospital are typically resistant to multiple antibiotics. A regimen that includes a beta-lactamase-resistant penicillin is usually combined with vancomycin and gentamycin, with or without rifampicin.

Infections due to Staphylococcus saprophyticus

S. saprophyticus is the second most common cause of *non-obstructive* urinary infection in sexually active females (*after E. coli*). The clinical symptoms are indistinguishable from those due to infection by other pathogens but the presence of gram-positive cocci in clumps in a urinary specimen assists and suggests the diagnosis. *S. saprophyticus* is susceptible to most antimicrobials used for treating urinary tract infection. The organism has been associated with renal calculi because of its capacity to produce urease.

Pneumococcal Infections

Microbiology *Streptococcus pneumoniae* is a gram-positive encapsulated diplococcus.[1] Several serotypes are described based on the antigenic character of the capsular polysaccharide. Types 3, 4, 14, and 19 predominate in clinical infections. The capsular polysaccharide renders the organism resistant to phagocytosis by polymorphonuclear cells, activates the alternate complement pathway[2] and along with the toxin pneumolysin mediates the clinical features of the illness.

Epidemiology Pneumococcus is the commonest cause of bacterial pneumonia worldwide. It is more prevalent at the extremes of age and in subjects with lymphomas, multiple myeloma, splenectomy, nephrotic syndrome, diabetes mellitus, cirrhosis and sickle cell disease. Infections are more common in winter and in early spring. The organism can spread from person to person by droplets but this is unusual.

Pneumococcal pneumonia

Pathogenesis Pneumococcal pneumonia begins with the colonisation of the nasopharynx by the organisms, followed by *microaspiration* or inhalation of the organisms into the lungs. In most normal subjects the mucociliary clearance mechanisms of the airways effectively clear the organisms. If these clearance mechanisms are altered, such as due to chronic bronchitis, preceding viral infections, conditions with a reduced immunoglobulin response, pneumonia results due to uninhibited proliferation of the organisms in the alveoli. Cough and sputum production, the cardinal symptoms of pneumonia, are due to the proliferation of bacteria in the alveoli and the inflammatory response elicited. Fever is a response to the release of cytokines such as interleukin-1 and tumour necrosis factor which are released locally and also systemically.

Clinical features Most cases of pneumococcal pneumonia have a subacute onset. In a minority, the disease has an acute onset with a single episode of *shaking chills* that last for upto 15 minutes—the so-called *classical* presentation. Often there may be an underlying condition that worsens, for example, increase in the amount of sputum and a change in its colour from white to yellow-green in a subject with chronic bronchitis. There may be a history of a preceding viral upper respiratory tract illness and then the temperature rises acutely to 38°C to 40.5°C. Cough may be initially dry but soon becomes productive with expectoration of purulent, blood streaked or *rusty* sputum. Pleuritic chest pain is a common symptom. Presentation in the elderly may be atypical with an insidious onset of

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[1] Found in groups of two, with adjacent surfaces being rounded and ends pointed to make a lancet shape

[2] See the chapter on Immune Diseases, for a description of complement pathways.

confusion, or abrupt onset of hypotension with hypothermia.

Patients with pneumococcal pneumonia appear sick, are febrile and have tachycardia (90–140/min) and tachypnea (20–35/min). Herpes labialis (fever blisters) may occur in a few patients. Findings on examination of the chest are dependent on the type of lung involvement. In *pneumococcal bronchopneumonia* there may only be *crackles.* In a lobar *consolidation,* the findings are *increased vocal and tactile fremitus, dullness to percussion, bronchial breath sounds and whispering pectoriloquy.*[1] Dullness to percussion, diminished breath sounds, a pleural rub, deviation of trachea to the opposite side and inability to detect the expected degree of diaphragmatic motion (on the basis of the patient's respiratory excursion) are all signs that suggest the presence of a *pleural effusion.*

Investigations There is evidence of neutrophilic leucocytosis (a majority have a white cell count >13,000/μL). Blood cultures are positive for pneumococcus in 15–30 per cent of patients. The simple investigation of choice is a Gram-stain of an adequate sample of expectorated sputum.[2] Gram-positive diplococci can be identified in up to 80 per cent of patients.

The chest X-ray reveals a subsegmental consolidation in the majority of patients. A segmental or lobar consolidation (with the typical air bronchogram) may also be seen but is less common.[3] A pleural effusion may be present in 20% but an empyema is formed in only 1–3%.[4]

Complications The development of an empyema, sepsis with hypotension, the adult respiratory distress syndrome, infection of contiguous sites (purulent pericarditis) and bacteremia with metastatic pyogenic disease (meningitis, arthritis, peritonitis) are potential complications which are quite uncommon.

Differential diagnosis[5] Though pneumococci are the commonest causes of community-acquired pneumonia, the possibility of infection with other pathogens should always be considered. Certain clues in the history, on physical examination and in the chest X-ray may suggest that infection is due to a particular organism (Table 8.6); but considerable overlap can exist in clinical presentation making microbiologic proof the critical evidence for infection with a particular agent.

Management The subject with a presumptive diagnosis of pneumococcal pneumonia can be managed on an outpatient basis unless there are specific indications for hospitalisation such as, 1) the presence of hypoxemia (PaO_2 < 50 mm Hg) or hypotension, 2) multilobar involvement,3) extremes of age, 4) multisystem involvement or 5) leukopenia (WBC count < 5000/μL). All of the above clinical features are poor prognostic factors.

Penicillin is the drug of choice and may be given orally (penicillin V 500 mg q 6 hrs) for 7–10 days. Parenteral regimens in the hospitalised patient include penicillin G (600,000 units i.v. q 4-6 hrs) or procaine penicillin (600,000 units i.m. q 12 hrs) for 7–10 days. Alternatives in the penicillin-allergic patients include erythromycin (500 mg–1 gram q 6 hrs i.v. or oral) and cephazolin (500 mg i.v. q 6 hrs). When concomitant meningitis or endocarditis is suspected on clinical grounds, the dose of penicillin G is increased (2 million units q 2 hours). Quinolones like ciprofloxacin are relatively ineffective against pneumococcus.

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[1] See chapter 11

[2] A specimen which has no epithelial cells and at least 15–20 WBCs in a microscopic field under × 1000 magnification

[3] Some authorities state that though pneumococcus is the commonest cause of lobar pneumonia, the commonest X-ray finding in pneumococcal pneumonia is a bronchopneumonia.

[4] Pneumococcus is the most common cause of empyemas, accounting for 15% of all empyemas, though empyema is an uncommon complication of pneumococcal pneumonia.

[5] See also chapter 11

Supportive measures include antipyretics, analgesics (for pain), proper hydration and an adequate diet. Most patients defervesce in 24–48 hours after start of antibiotics. *Failure of the temperature to normalise after 4 days of antibiotic therapy in the presence of persistent leucocytosis indicates the possibility of a complication like empyema.* Empyema may be distinguished from the more common *parapneumonic* (sympathetic) effusions by the demonstrations of organisms either on Gramstain or in pleural fluid cultures.

Drug resistance to penicillin is encountered in less than 5 per cent of patients and under these circumstances vancomycin is the preferred agent.

Prevention A vaccine containing 25 μg of capsular polysaccharide of each of 23 serotypes of pneumococcus, is available for prophylaxis of adults at an increased risk of infection: patients with lymphoma, myeloma, asplenia, sickle cell disease, HIV infection, chronic bronchitis, elderly subjects (more than 65 years age). Vaccination should be repeated at an interval of 5 years.

Pneumococcal meningitis

S. pneumoniae is the second most common cause of meningitis in adults (meningococcus being the commonest) and in children above the age of 5 years (*H. influenzae* being the commonest). Sinusitis, head injury (which tears the dura mater allowing the direct entry of organisms) and CSF leaks predispose to pneumococcal meningitis.

Rapid onset of fever, headache, neck pain and altered sensorium characterise pneumococcal meningitis. The absence of a rash and the increased frequency of cranial nerve palsies and focal neurologic deficits serve to distinguish pneumococcal meningitis from meningococcal disease. Clinical distinction between meningitic syndromes due to different organisms may be difficult and only microbiologic identification of the pathogen is diagnostic.

The cerebrospinal fluid shows neutrophilic leucocytosis (>1000 WBC/μL), a low glucose level (<40 mg/dL, or <50% serum levels) and elevated protein levels (>150 mg/dL). A Gram-stain of cerebrospinal fluid shows gram-positive diplococci in 80–90% of patients. Antigen detection by counter-immunoelectrophoresis may be a useful adjunct for the rapid diagnosis of pneumococcal meningitis.

Penicillin G (24 million units i.v. in 6 divided doses) for 2 weeks is the treatment of choice. Ceftriaxone (4 g/day in 2 divided doses), chloramphenicol (6 g/day in 4 divided doses) or vancomycin (1 gram i.v. q 12 hours) are alternatives in the penicillin-allergic patient or in infection due to penicillin-resistant organisms. Adjunctive steroids (dexamethasone 0.15mg/kg) may be administered in the presence of focal neurologic deficits, coma or increased intracranial pressure.

Other pneumococcal infections

Pneumococci are the commonest cause of acute otitis media in children and a frequent cause of acute sinusitis. Complications of otitis media include mastoiditis, meningitis and lateral sinus thrombosis. Primary pneumococcal peritonitis is an infection found in girls, presumably due to ascending infection from the vagina through the fallopian tubes. It is also common in patients with nephrotic syndrome.

Other infections due to gram-positive bacteria are summarised in Table 8.7

DISEASES DUE TO GRAM-NEGATIVE BACTERIA

Meningococcal infection

Epidemiology Meningococcal infection is common among young children, especially those below the age of 1 year. Seven serotypes of *Neisseria meningitidis* are recognised (A,B,C,D,X,Y,Z). The clinical disease is most often due to type B, whereas epidemics are due to type A. The organism spreads from person to person by way of nasopharyngeal secretions. The rates of infection are higher among house-

Table 8.6 Differential diagnosis of a community-acquired pneumonia

Clues	*Possible pathogen*
History	
epidemic in a training camp	S. pneumoniae, Chlamydia pneumoniae
exposure to livestock	Coxiella burnetti
exposure to psittacine birds*	Chlamydia psittaci, Coccidiodes immitis
exposure to contaminated bat caves	Histoplasma capsulatum
health care worker	Mycobacterium tuberculosis
stay in a hotel (with air conditioning)	Legionella pneumophila
prominent gastrointestinal features of onset	Legionella pneumophila
seizures, aspiration or diminished gag	Anerobes, polymicrobial
Host factors	
HIV infection	Pneumocystis carinii, Mycobacterium tuberculosis, S. pneumoniae, H. influenzae
alcoholism, diabetes	S. pneumoniae, Staphylococcus aureus, Klebsiella pneumoniae
chronic obstructive pulmonary disease	S. pneumoniae, H. influenzae
immunosuppressed states	Cytomegalovirus, P. carinii, Legionella pneumophila
Physical findings	
bullous myringitis, erythema multiforme, cerebellar ataxia or encephalitis	Mycoplasma pneumoniae
erythema nodosum	Mycobacterium tuberculosis
halitosis, foul smelling sputum	Anerobes
Unusual X-ray findings	
miliary mottling	Mycobacterium tuberculosis, H. capsulatum, C. immitis
interstitial shadows	Viruses, P. carinii, C. psittaci, M. pneumoniae
hilar lymphadenopathy	Mycobacterium tuberculosis, C. psittaci, Francisella tularensis, Epstein-Barr virus, M. pneumoniae, Fungal
cavitation	Mycobacterium tuberculosis, anerobes, L. pneumophila, Atypical mycobacteria, Nocardia
pneumatocoeles	S. aureus, S. pyogenes, P. carinii

* Psittacine birds refers to parrots, ducks and chicken.

Table 8.7 Uncommon infections of adults due to gram-positive bacilli

Disease	*Etiology*	*Epidemiology*	*Symptoms*	*Diagnostic tests*	*Treatment*
Erysipeloid (of Rosenbach)	Erysipelothrix rhusiopathiae	occupational disease; occurs after exposure to infected animal	raised, indurated purple-red maculopapule; burning and itching; local swelling; hand affected most often	culture of needle aspirate from lesion	Benzathine penicillin 1.2 million u im or Erythromycin 500 mg qid x 7 days
Anthrax (Woolsorter's disease; malignant pustule)	Bacillus anthracis	occupational disease of farmers, butchers; acquired from infected sheep, cattle, goats	• **cutaneous anthrax**: erythematous papule which vesiculates and finally ulcerates to form a black eschar; fever, malaise • **gastrointestinal anthrax**: abdominal pain, sepsis • **pulmonary anthrax**: fever, dyspnea, pulmonary edema, pleural effusion	Gram-stain of smears and cultures (skin lesion, sputum or stool)	Procaine penicillin 600,000 u im bid × 7 days (cutaneous form) Penicillin G 4 million u q 6 hrs or ciprofloxacin (extracutaneous forms)
Listeriosis	Listeria monocytogenes	acquired by ingestion of infected dairy products or raw vegetables; immunosuppressed states; transplacental transmission	• **meningoencephalitis:** commonest form, fever, headache, delirium • **typhoidal form**: high fever without localisation • **oculoglandular form**: conjunctival inoculation with ophthalmitis	Gram-stain of CSF or meconium	Penicillin G 75,000 u/kg iv q 4 hrs × 14 days (meningitis) Penicillin G as above + tobramycin 1.7 mg/kg iv q 8 hrs x 4 weeks (typhoidal form)

Table 8.7 Uncommon infections of adults due to gram-positive bacilli (contd.)

Disease	*Etiology*	*Epidemiology*	*Symptoms*	*Diagnostic tests*	*Treatment*
Nocardiosis	Nocardia asteroides	acquired by direct contact with contaminated soil; immunosuppressed states	• **pulmonary**: cough, fever, weight loss • **skin or subcutaneous:** abscesses • **metastatic** abscesses: brain abscess	microscopic examination of pus, sputum or CSF	Sulfonamide (1 g iv q 4 hrs or oral or trimethoprim-sulphamethoxazole 6 tab qid oral
Actinomycosis	Actinomyces israelii	adult males; portal of entry: decayed tooth, aspiration of oral secretions or breach of intestinal mucosa	• **abdominal form**: cecum and appendix; right iliac fossa mass with sinuses discharging to abdominal wall; fever, diarrhea, constipation, intestinal obstruction • **cervicofacial**: jaw lump with sinuses discharging sulphur granules • **thoracic**: pulmonary lesion resembling tuberculosis with cutaneous sinuses • **localised uterine**: due to infected IUD	Gram-stain of sulphur granules demonstrate filamentous forms that are gram-positive	Penicillin G 10–20 million u/day iv × 4–6 wks followed by Penicillin V 2–4 g/day oral × 6–12 months OR Ampicillin 50 mg/kg/day iv × 4–6 wks, followed by 0.5 g tid po × 6 months
Diphtheria	Corynebacterium diphtheriae plus β bacteriophage which upon lysogenising the bacteria enable it to produce exotoxin	acquired by direct contact with patient, carriers or by ingesting raw milk	sore throat, nasal discharge, fever, patch in throat (pseudomembrane), hoarseness • **complications:** myocarditis (2nd wk) and neuritis (3rd to 6th wk)	Gram-stain of membrane reveals gram-positive rods with metachromatic granules and a Chinese lettering pattern	Diphtheria antittoxin 20,000–100,000 u iv after skin test; must be given early procaine penicillin 600,000 u im q 12 hrs OR erythromycin 500 mg q 6 hrs x 7 days

hold contacts, alcoholics, patients with deficiency of the terminal complement components (C5,6,7,8) and in overcrowded environments.

Pathogenesis The infection is acquired throughout the aerosol route. The organism localises initially in the nasopharynx. After an incubation period of 3–4 days, bacteremia occurs and the organism disseminates to the joints, meninges, adrenal glands and the skin. Bacterial exotoxins result in tissue necrosis, hemorrhage and vascular thrombosis. Tissue damage results in clinical symptoms of the disease.

Clinical features *Meningococcal bacteremia* is associated with the sudden onset of spiking fever, headache, malaise, myalgia, arthralgia and a generalised rash. The rash may be maculopapular, petechial or even nodular. A small proportion (10–20%) of these bacteremic patients progress to fulminant meningococcemia. In these patients there is extreme prostration, hypotension and a hemorrhagic rash. This syndrome (also called the *Waterhouse-Fri derichsen syndrome*) is associated with a very high mortality. Death results from respiratory failure or heart failure, often over the course of a few hours.

Chronic meningococcemia is a rare condition associated with intermittent fever, arthritis, a maculopapular rash and palpable splenomegaly.

Meningococcal meningitis is a condition affecting children between the ages of 6 months and 10 years. The disease presents with high fever and pain in the neck. The clinical presence of stiffness in the neck and a petechial rash make the diagnosis of meningococcal meningitis highly likely.

Complications of meningococcal meningitis include occurrence of seizures during the acute phase and residual nerve palsies (deafness in upto 10%). Polyarticular arthritis occurs as a complication of meningococcemia (seen in 2–10% of patients).

Diagnosis The diagnosis of meningococcal infection is based on the isolation of the organism from blood, CSF, skin rash scraping, or joint fluid; gram-negative cocci are typically seen which can be differentiated from gonococci by microbiologic testing. All specimens must be promptly processed as the organism is very sensitive to temperature; the CSF should not be refrigerated. The nasopharyngeal presence of the organism does not necessarily constitute evidence of infection as the organism frequently colonises the pharynx. The peripheral blood shows neutrophilic leucocytosis. Patients with meningitis show a low CSF glucose (usually <35 mg/dl), elevated proteins and prominent polymorphonuclear cells (100–10,000/mm^3). A Gram-stain will identify the organism in over 50 per cent of the patients. A rapid latex particle agglutination test is also available for the rapid diagnosis of meningococcal meningitis.

Treatment Prompt supportive care, immediate institution of antibiotic treatment and careful vigilance for development of complications are needed for the effective treatment of patients with meningococcal illness. Proper hydration should be maintained and adequacy of ventilation ensured. Monitoring arterial blood gases and fluid status (use of a central venous line) is important for managing the hypotensive patient. Penicillin G (12–24 million units/day divided into 4 hourly doses) for 7–10 days, is the treatment of choice. In penicillin-allergic patients, chloramphenicol (4–6 g/day, in 4 hourly doses) or third-generation cephalosporins may be used. Cefotaxime (50 mg/kg i.v. q 6 hours, not to exceed 12 g/day) or ceftriaxone (75 mg/kg i.v. initial dose followed by 50 mg/kg i.v. q 12 hours, not exceeding 4 grams/ day) are highly effective against meningococci. Antibiotic treatment for meningitis is usually continued for at least 4–5 days after the patient becomes afebrile. Steroids (0.15 mg/kg q 6 hours for 4 days, started 15–20 minutes prior to antibiotic treatment) are additionally indicated in meningitic illness in order to reduce morbidity

and mortality and to prevent complications of the illness.

Prophylaxis Prophylaxis is recommended for household contacts. Effective drugs include rifampicin (600 mg or 10 mg/kg [children] q 12 h for 4 doses), spiramycin (500 mg or 10 mg/kg [children] oral q 6 h for 5 days) or ceftriaxone (single intramuscular dose of 250 mg [125 mg in children]).

Hemophilus Influenzae Infections

Microbiology H. influenzae are small non-motile, non-spore-forming organisms that appear as small, pleomorphic gram-negative bacilli. H. influenzae requires the presence of X factor (hematin) and the V factor (nicotinamide adenine dinucleotide [NAD]) for growth in the culture media. H. influenza strains may be encapsulated (typable) or unencapsulated (non-typable). There are six different serotypes of the encapsulated strains, *Types a* to *f*. These serotypes can be distinguished by means of serologic tests on the basis of antigens present in their polysaccharide capsules. A majority of infections due to Hemophilus in children (including meningitis) are caused by one specific serotype, H. influenzae Type b. This serotype is particularly pathogenic because of the anti-phagocytic activity of its capsular polysaccharide polyribosyl ribitol phosphate (PRP). Non-typable H. influenzae are frequent respiratory tract colonisers in patients with chronic obstructive pulmonary disease (COPD) and commonly exacerbate chronic bronchitis in these patients. Non-typable strains are also among the most common causes of acute otitis media in children.

Epidemiology and pathogenesis H. influenzae bacilli are endemic worldwide. The organisms colonise the upper respiratory tract mucosa. Antibodies against PRP are necessary for the clearance of these organisms from the blood stream by the reticuloendothelial system. The ability to form antibody to PRP increases with age. This explains the greater virulence of the organism in very young children. Additional host factors that are associated with an enhanced susceptibility to H. influenzae infection include immunoglobulin deficiencies, asplenic states, sickle cell anemia, chronic cerebrospinal fluid fistulae, and chronic pulmonary infections.

Clinical features and diagnosis H. influenzae is the leading cause of pyogenic meningitis and bacterial epiglottitis in children. The organism also causes bronchopulmonary and invasive bacteremic infections in this age group. In children, serious infections such as pyogenic meningitis, epiglottitis, and facial cellulitis should suggest H. influenzae as the possible etiology.

Meningitis: Other than the particular age-group involved (<3 years), meningitis due to H. influenzae cannot be clinically differentiated from that due to other organisms. Type b organism is the causative agent. The organism enters the vascular choroid plexus usually through the nasopharynx. An episode of otitis media initiates meningeal infection.

Epiglottitis: H. influenzae is also the leading cause of epiglottitis in children between two to four years of age. Fever, drooling and stridor are characteristic features.

Otitis media and sinusitis: After Strep. pneumoniae, H. influenzae is the most common cause of bacterial acute otitis media in young children. Acute sinusitis is more common in adults.

Arthritis: H. influenzae type b is also the most common cause of septic arthritis in children below the age of two years.

Pneumonia: H. influenzae pneumonia occurs principally in adults with underlying chronic lung disease. Clinically, the disease cannot be distinguished from that due to other causes of bacterial pneumonia; however, a broncho-pneumonic pattern and parapneumonic effusions are more common with H. influenzae pneumonia.

The diagnosis of H. influenzae infection is suspected by the finding of gram-negative pleomorphic coccobacilli on a Gramstain of the exudate or infected body fluid (such as CSF). A rapid latex particle agglutination test is available to confirm infection of the cerebrospinal fluid.

Treatment When H. influenzae is the suspected cause of meningitis or invasive infection in children, the initial treatment should consist of chloramphenicol (1 g i.v. q 4 hours), either alone or combined with ampicillin (2 g i.v. q 4 hours) or a third-generation cephalosporin (for example, cefotaxime [50 mg/kg i.v. q 6 hours, not to exceed 12 g/day] or ceftriaxone [75 mg/kg i.v. initial dose followed by 50 mg/kg i.v. q 12 hours, not exceeding 4 g/day]), while awaiting laboratory sensitivity results. If the organism does not produce β-lactamase, ampicillin can be given as monotherapy. Although chloram-phenicol is generally only bacteriostatic, it is bactericidal against H. influenzae Type b and is an effective alternative. Steroid (dexamethasone 8 mg i.m. q 12 hours for 3 days) are used as adjuvant therapy in meningitic illness to reduce the incidence of complications. Ampicillin is the preferred drug in the initial treatment of adults with pneumonia due to H. influenzae.

Prevention Prophylactic rifampicin (20 mg/kg orally once daily for four days) is recommended for all other members of the household if there is at least one contact who is younger than four years and provided the index case had the illness within the preceding two weeks.

With the availability of potent polysaccharide protein conjugate vaccines effective for immunisation against H. influenzae, it is recommended that all children should be vaccinated beginning at the age of two months. The recommended schedule consists of 2–3 initial doses (2 months apart) followed by a booster dose at 12 months of age.

Other Hemophilus infections

Other Hemophilus species (besides H. influenzae) can also be pathogenic. H. aegyptius[1] strains have been isolated from conjuctivitis patients. This strain has also been implicated as the cause of Brazilian purpuric fever. H. ducreyi is the causative organism of chancroid. This entity is discussed in detail in the section on sexually transmitted diseases.

Typhoid Fever

Typhoid[2] refers to an acute systemic illness caused by infection with *Salmonella typhi* which is characterised by prolonged fever, prostration, a sustained bacteremia (without endothelial or endocardial involvement) and hyperplasia of the reticuloendothelial system. Typhoid fever is the prototype of enteric fever—a term used for a similar syndrome due to infection with *S. typhi, S. paratyphi A, B (S. schottmuelleri), C (S. hirsch-feldii)* or *S. sendai.*

Epidemiology *S. typhi* infects only humans; all cases of typhoid should, therefore, be traced to another infected human being. The major source of the infecting organism is the stool or urine of carriers of the disease or of recovering cases. Fecal carriers outnumber urinary carriers by a ratio of 10 to 1. The commonest mode of acquiring the infection is by the *ingestion of contaminated food* or water. Direct fecal-hand-oral contact is an uncommon mode of transmission. Food is infected by water used to wash it, by the hands of carriers, by fomites or by flies. *S. typhi* can survive in water, ice, milk or milk products and dried sewage for several weeks. The incidence of the disease peaks in the hot dry months of the year when the concentration of organisms is high (undiluted by rain). A peak may also be seen during the rainy season when flooding leads to sewage contamination of drinking water. Though

[1] Previously called the Koch-Weeks bacillus, because of their hemagglutinating property, these strains are now considered to be H. influenzae.

[2] From the Greek word 'typhos' meaning smoke; refers to the apathy and confusion that are prominent features of the fully developed syndrome

hospital-based series note a high incidence among adolescents and young adults, outpatient studies indicate a peak incidence rate in children between 3 to 9 years of age; this reflects the fact that the disease is more severe in adults, necessitating hospitalisation more frequently. Typhoid fever is 2 to 3 times more common as compared to paratyphoid fever in developing countries.

Etiopathogenesis and pathology *S. typhi* is a gram-negative, non-encapsulated, non-sporing flagellated rod which has a somatic (O) antigen (an oligosaccharide), a flagellar (H) antigen (a protein), a polysaccharide envelope (K or V_1) antigen and a lipopolysaccharide *endotoxin* that forms its outer cell wall. After ingestion the organisms attach to the tips of the villi in the jejunum and ileum. The organisms penetrate the mucosa through unknown mechanisms and pass to the intestinal lymphoid follicles, and from there to the mesenteric lymph nodes. They multiply within the mononuclear cells of the lymph follicles and some pass into the systemic circulation to sequestrate and multiply within the reticuloendothelial cells of the liver and spleen. About 7 to 14 days after the initial entry (*incubation period*), a sufficient number of bacteria are released from their intracellular habitat within the lymphoid cells into the thoracic duct and from there into the systemic circulation. During this *bacteremic phase* of the illness, the organisms can be found in almost all the organs. Within the tissues, the salmonellae evoke a typical reaction characterised by aggregates of macrophages (containing intracellular bacilli)– the *typhoid nodules.* In the spleen, the red pulp is congested and filled with typhoid nodules rendering the organ palpable. Within the liver, there is focal cloudy swelling of hepatocytes and hyperplasia of Kupffer cells. Intestinal changes are especially prominent in the *Peyer's patches* of the ileum; typhoid nodules are common and the lymphoid tissue is hyperplastic. If the changes do not resolve, mucosal necrosis develops in the second week of clinical illness. Sloughing of mucosa results in typical ulcers that are found along the antimesenteric border and conform in shape and location to the distribution of lymphoid follicles. The ulcers may perforate into the peritoneal cavity; the majority of ulcers are single and small (<1 cm) and lie within 60 cm from the ileocecal valve.

The systemic features of typhoid are presently felt to be related to the release of various *cytokines* into the circulation by the infected macrophages rather than due to endotoxemia. These cytokines include *tumour necrosis factor, interleukin-1,* and *interferons.*

Clinical features Fever is the cardinal feature of typhoid. Though a stepwise rise has been classically described, it is infrequently found; sustained and remittent patterns of fever are common. Generalised malaise and anorexia are universal. Dull frontal headaches are frequent (85%). Patients frequently complain of dull ill-localised abdominal discomfort (50%). Both diarrhea (45%) and constipation (40%) are frequent. Diarrhea is more common in the second week of illness when intestinal lesions are florid. A non-productive cough and symptoms referable to the upper respiratory tract can be seen in about 20 per cent of patients. Neuropsychiatric manifestations are common in our country (5–15%) and comprise a wide spectrum of findings ranging from disorientation to delirium (*enteric encephalopathy*), obtundation, stupor or coma.

On physical examination, the patient is febrile and about 10–15% may appear severely toxic. Relative bradycardia, once emphasised as a cardinal feature, is infrequent (<25%). *Rose spots* are quite infrequent in dark skinned people; when found in fair subjects, they are blanching maculopapular, measuring 2–4 mm and found mostly on the abdomen and chest. These spots occur in crops of 5 to 15 in the second week of the illness and disappear in 2 to 5 days. The tongue is covered with a white-

brown coating that spares the tips and the margins (90%). The spleen is usually palpable (2 to 3 cm below the left costal margin) and soft in upto 40% of subjects. A soft hepatomegaly (2–3 cm) is more frequent being found in upto 50% of subjects. Abdominal palpation may reveal a *doughy* feel; it reflects the feeling of loops of bowel filled with air and fluid due to *localised ileus.* The percussion component of this finding is a *tympanitic* note. Diffuse abdominal tenderness may be seen and differentiation from a perforation may be difficult in the absence of frank *guarding.*

Complications

Intestinal hemorrhage: Intestinal bleeding is not uncommon in typhoid. Occult blood in the stools can be detected in 20 to 30 per cent of patients; the stool contains gross blood in 10 per cent. Severe bleeding occurs in about 2 per cent and carries a high mortality (25%). Bleeding usually occurs during the third week of illness.

Intestinal perforation: Intestinal perforation occurs in about 1–2 per cent of patients and also usually in the third week of illness. A clinical finding of sudden onset of severe pain in the right lower quadrant, with absent bowel sounds (50%) and guarding, rebound tenderness and rigidity (75%) strongly suggests the diagnosis. Less classical presentations are known with only diffuse abdominal tenderness (25%). A rising pulse rate, a fall in blood pressure or a rise in white cell count with a shift to left should alert the physician to the possibility of this complication.

Rare complications of typhoid include acute cholecystitis (2%), myocarditis (1%), pneumonitis (1–5%), focal infections (osteomyelitis, soft tissue abscess, parotitis), immune complex glomerulonephritis and pyelonephritis. Spontaneous abortions and premature labour are common in pregnant women with untreated typhoid.

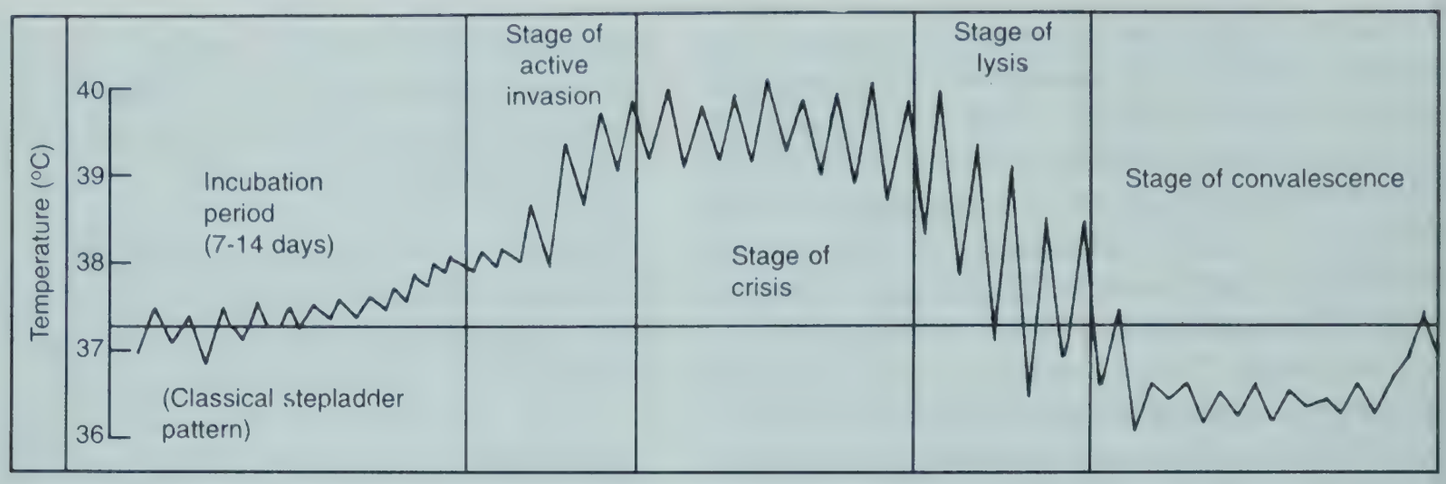
A relapse of enteric fever occurs in 5 to 15% of treated and untreated patients. It usually manifests as recurrence of fever about two weeks after initial defervescence. The relapse is more common in treated patients presumably due to the inhibition of an effective natural immune response to the organisms (resulting from their prompt elimination).

Diagnosis The diagnosis of typhoid (Fig 8.7) is based on the proof of infection by *Salmonella* in an individual with a suggestive clinical illness. Routine tests may reveal anemia (partly related to occult enteric blood loss) and leukopenia. Leukocytosis is unusual in typhoid and suggests either a complication (such as perforation) or a metastatic infection. Blood cultures are positive in the second week of the illness while stool cultures are positive in the third to fifth weeks. Indirect evidence of typhoid infection may be obtained from the serologic agglutination test—*Widal test.* Typhoid antigens contain antigens (O and H) which stimulate specific antibody synthesis; a fourfold rise in titres are suggestive. However, the test is only 60 per cent sensitive and not specific. Vaccine administration, any inflammatory condition[1] (such as chronic active hepatitis), hepatic cirrhosis and infection with non-typhoidal *Salmonella* strains (that share the antigens can yield a positive Widal test. Some individuals who are treated early during the course of the infection do not mount an antibody response.

The other illnesses to be considered in the differential diagnosis of enteric fever include malaria, tuberculosis (disseminated), brucellosis and other bacteremias.

Management The drugs used in the treatment of typhoid fever and their doses are listed in Table 8.8. In the very toxic patient, glucocorticoids may be added to the treatment regimen. Dexamethasone (3 mg/kg i.v. initially followed by 1 mg/kg q 6 hours for 48 hours) has been shown to improve the outcome in patients with enteric encephalopathy or shock. Aspirin

[1] The rise in antibodies to Salmonella with other infections is called an anamnestic response: the body produces antibodies against antigens it was previously exposed to on being challenged with other closely related pathogens.



	Week of disease	1st week	2nd week	3rd week	4th week	beyond 4th week
Pathology	Organisms increasing in number and firmly establishing infection	• bacteremia • proliferation within gut lymphoid tissue	• focal necroses and ulceration of intestines • typhoid nodules liver and spleen • mononuclear vasculitis (skin)	bodily defenses overcoming organisms	• stage of repair and recovery from parenchymatous degeneration • chronic fecal carriage • metastatic foci	
Symptoms	asymptomatic, diarrhea in 10%	fever, headache, constipation, sore throat	rash, abdominal pain, diarrhea, delirium	complications: hemorrhage, perforation	resolution of symptoms relapse	
Signs	none	abdominal tenderness	rose spots, splenomegaly, hepatomegaly	melena, ileus, guarding	cholecystitis, osteomyelitis, soft tissue abscesses	

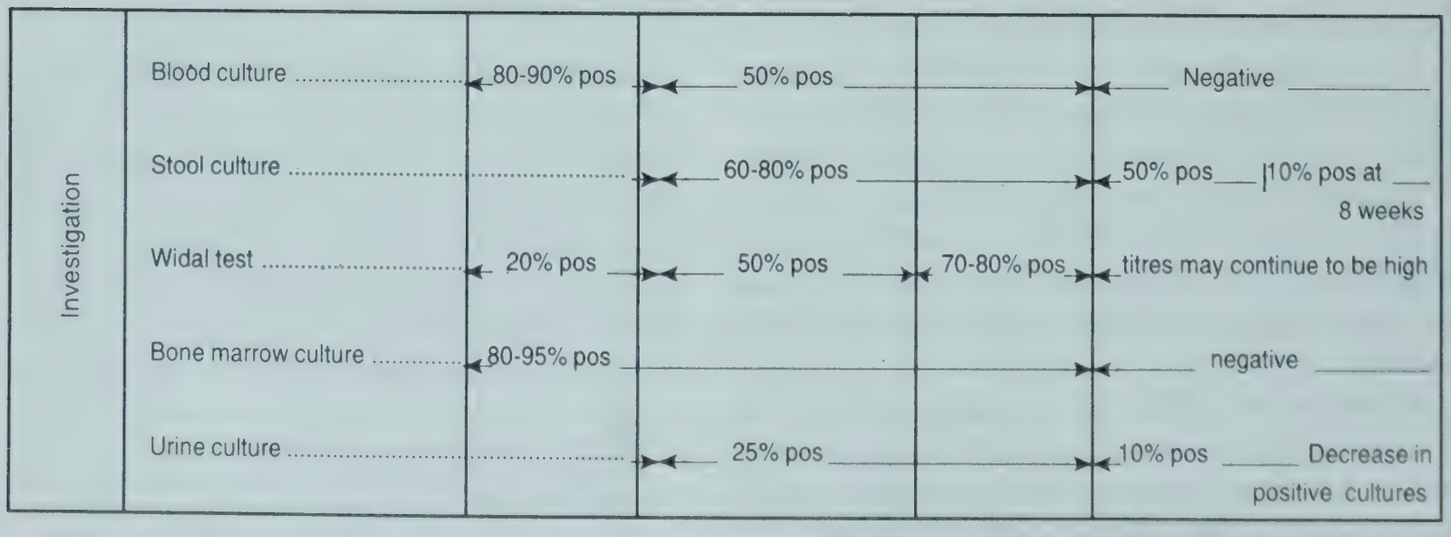


Fig 8.7 Typhoid fever: clinicopathologic correlation and temporal profile

Table 8.8 Treatment of Salmonella typhi infection

Disease category	Drug	Daily dose	no.of doses	Duration	Cure rate	Effect on relapse rate	Comments
(A) **Enteric fever**							
	1. Chloramphenicol	50 mg/kg oral or i.v.	4	14 days*	90%	nil (relapse rate 5–14%)	• no effect on convalescent carrier • causes aplastic anemia 1 in 10,000 to 1 in 50,000 • not useful for treating plasmid mediated resistant strains • more rapid defervescence as compared to 2 & 3.
	2. Trimethoprim-sulfamethoxazole	6.5 mg–10 mg/kg of trimethoprim; approx 640 mg Trimethoprim and 3200 mg sulfamethoxazole oral or i.v.	2	14 days	90%	decrease	lowers convalescent excretor rate
	3. Ampicillin	100–150 mg/kg oral or i.v.	4	14 days	90%	decrease	lowers convalescent excretor rate
	4. Amoxicillin	75–100 mg/kg oral	4	14 days**	90%	decrease	lowers convalescent excretor rate
	5. Ceftriaxone	50–60 mg/kg/d i.v. or i.m.	2	14 days**	>90% (92-95%)	? (possibly very low	clinical experience is increasing
	Cefoperazone	100 mg/kg/day i.v. or i.m.	2	14 days**	90%	relapse rate)	defervescence in 2–5 days
	6. Ciprofloxacin	500 mg bd oral	2	14 days	>90% nearly 100%	? (no relapse reported)	defervescence in 3–5 days, not recommended for prepubertal children
(B) **Chronic carrier**							
Without gallbladder disease	1. Ampicillin or Amoxicillin	100 mg/kg/day oral or i.v.	4	28 days	60%		
	+						
	Probenecid	30 mg/kg/day oral	4	28 days			
	2. Trimethoprim-Sulfamethoxazole	160 mg/800mg oral bd	2	42 days			
	+						
	Rifampicin	600 mg oral	1	42 days			
	3. Ciprofloxacin	750 mg bd oral	2	28	80%		
With gall bladder disease	1 or 2 or 3 above + Cholecystectomy				80–90%		

* Some authorities recommend halving the daily dose after the patient has been afebrile for 2 days.

** 5 day regimens have been reported to be as effective. Cephalosporins and quinolones *recommended* in areas with high prevalence of multidrug-resistant S. typhi.

should not be used as an antipyretic because it can increase the risk of intestinal hemorrhage.

Proper nutrition should be ensured. Bland soft diets or porridge meals are not required. Thorough handwashing and fecal disposal are of paramount importance to prevent cross-infection of other family members by the feco-oral route.

Complications occur in the third week and patients are observed carefully during this period. Intestinal hemorrhage and small localised perforations can be managed conservatively with transfusions, antibiotics and intensive monitoring. Generalised peritonitis due to perforation may require surgical intervention (suture of perforation without bowel resection). Relapses are treated with the same regimen as the primary infection and generally respond within 5 days. The treatment of carriers is outlined in Table 8.8.

Prevention The prevention of typhoid requires purification of drinking water, detection and treatment of carriers and effective disposal of sewage. Raw vegetables must not be eaten as such and water should be boiled if it is not known to be clean and pure. A parenteral-killed vaccine (administered intradermally) and an oral live vaccine (Ty 21a) are available for travellers visiting endemic areas.

Shigellosis (Bacillary Dysentery)

Shigellosis[1] is an acute infection of the lower intestinal tract caused by organisms belonging to the genus *Shigella.* The infection takes the form of a spectrum of manifestations that range from *subclinical* infection and *mild watery diarrhea* to *fulminant dysentery.*

Etiopathogenesis Shigellae are non-motile gram-negative bacilli belonging to the family *Enterobacteriaceae* and consist of four species: *S. dysenteriae* is the prototype which produces the most severe illness, exhibits pandemic behaviour, is the only one to produce a potent exotoxin (*Shiga toxin*[2]) and is especially difficult to cultivate. *S. sonnei* is the most common isolate in developed countries and causes mild (*catarrhal*) illness. *S. flexneri* and *S. boydii* are the two other species; the former causes a severe illness and the latter is restricted to the Indian subcontinent in distribution. The major site of pathology is the lower half of the colon, though in severe disease the entire colon and the terminal ileum may be involved. The intraepithelial proliferation of the organisms is followed by the death of the enterocytes and the consequent development of small mucosal ulcers. The bacilli are released into the *lamina propria* where they provoke an intense polymorphonuclear cellular response resulting in the formation of *microabscesses* within the intestinal crypts. Bacteremia is found in 10 per cent of patients. *S. dysenteriae* elaborates an enterotoxin that inhibits protein synthesis and induces *intestinal secretion.* Enterotoxin-associated disease results in systemic features like toxemia and high grade fever. One of the feared complications of shigellosis, the *hemolytic-uremic syndrome,* is attributed to the effects of the Shiga toxin.

Epidemiology Shigellosis is endemic among preschool children in tropical countries. An average child in the tropical countries develops between 3 to 6 episodes of diarrhea in a year and it is estimated that about 10 per cent of these episodes are due to the Shigella species. Humans are is the only natural hosts and reservoirs of infection. Shigellosis is characterised by *ready transmissi-bility* with very few organisms.[3] Direct *fecal-hand-oral* contact is the principal route of transmission; 20 per cent of adult household

[1] Strictly speaking bacillary dysentery means the presence of blood and mucous in the stools due to bacterial invasion. The term has become synonymous with Shigellosis as Shigella is the most common cause of the syndrome.

[2] Sometimes called a neurotoxin as it can produce hind limb paralysis in laboratory animals. Other species can elaborate small amounts of this toxin.

[3] As few as 200 organisms can cause overt disease in human volunteers.

contacts and 40 per cent of children within the household acquire the disease. Indirect spread is possible by contaminated food or by flies serving as mechanical vectors; water-borne forms are uncommon. A sexual mode of transmission has been identified among homosexuals. *Infection does impart immunity* but its nature is unclear. Reinfection with the same strain is possible. Pandemics due to drug-resistant strains of S. dysenteriae occurred in south India in the years 1974–1978 and in the eastern parts of India and Bangladesh in the mid-1980s.

Clinical features The incubation period of shigellosis is typically 1 to 4 days. The illness ranges in severity from a subacute onset of watery diarrhea to a fulminant dysentery. In children, the onset is often sudden with high grade fever, abdominal pain, vomiting and an initial non-bloody watery diarrhea. Over the next 48 hours, blood and pus appear in the stools and the stool frequency may increase to upto 20 or more per 24 hours. Convulsions may occur early in the disease. Severe mucosal ulceration can result in significant dehydration and pronounced blood loss.

Adults present with griping abdominal pain, tenesmus and an urgency to defecate. Stools are often formed in the initial stages but soon diarrhea becomes more marked.

Complications Complications of the disease are mainly restricted to infants and children under 2 years. Significant dehydration, convulsions, the *hemolytic-uremic syndrome,* a leukemoid reaction, rectal prolapse and severe hypoproteinemia are occasionally encountered. An association with Reiter syndrome has been described in adolescents who are HLA-B27 positive.

Diagnosis and differential diagnosis Mild diarrheal illness due to Shigella may be indistinguishable clinically from that due to other bacterial, viral or protozoal agents. A specific diagnosis can be established only by culturing the organism from the stool specimen. A non-specific but simple and essential test is to examine a drop of stool mucous mixed on a slide with a drop of saline, smeared and lightly heat fixed and stained with methylene blue. An abundance of polymorphonuclear leucocytes helps differentiate the condition from amebic dysentery; in amebic dysentery the trophozoites can be seen and leucocytes are scarce (amebae destroy the leucocytes). Sigmoidoscopy can also help in distinguishing the two conditions; in shigellosis the ulcers are *punched* out whereas in amebiasis they are *undermined.* Sigmoidoscopic swabs should be cultured immediately and examined microscopically for the presence of amebic trophozoites.

Treatment In shigellosis, as in any diarrheal illness, proper hydration is the mainstay of therapy. Agents that decrease intestinal motility (opiates, loperamide) are to be avoided as they can prolong the course of the disease as well as the duration of fecal excretion of the organism. Antidiarrheal preparations such as kaolin-pectin formulae or bismuth compounds are neither beneficial nor harmful and are best avoided. Untreated mild disease leads to spontaneous recovery in 5–7 days. Specific antimicrobial treatment has been shown to decrease the duration of fever, duration of illness, and the fecal excretion of the organism. The drug of choice is trimethoprim (160 mg)-sulfamethoxazole (800 mg) administered every 12 hours for 5 days. Nalidixic acid in a dose of 55 mg/kg/day for 5 days is equally effective. Other alternatives include the quinolones[1] (norfloxacin 400 mg bd or ciprofloxacin 500 mg bd) or furazolidine (5 mg/kg/day) for 5 days. Tetracyclines and ampicillin are avoided as resistance to these drugs is fairly widespread. Amoxycillin is avoided as it is not effective in shigellosis.

[1] To be used in patients above 17 years; quinolones can affect cartilage growth in younger people.

Prevention Health education with an emphasis on washing hands with soap after each defecation is of paramount importance (given the knowledge that humans are the only hosts who are affected and that Shigella spreads readily with very low infecting doses). All individuals who handle food must be appropriately instructed. The soiled clothes of affected individuals must be immersed in covered soap water buckets until they can be boiled. A live oral vaccine is currently undergoing field trials.

Cholera

Cholera is an acute infection of the entire small bowel due to *Vibrio cholerae* which is characterised by profuse watery diarrhea, vomiting and dehydration.

Microbiology and pathogenesis *Vibrio cholera* is a curved, motile gram-negative rod that has several serotypes and two biotypes. The two biotypes of serogroup 01 are the *classical* form and the *El Tor* form. Variable phage susceptibility and a resistance to polymyxin B identify the *El Tor* biotype. The El Tor biotype causes a more mild and often asymptomatic illness as compared to the classical biotype. Though earlier epidemics of cholera were due to the serogroup 01, presently the pandemic raging through India is believed to be due to a *non-01 serogroup (0139* serogroup).

The toxicity of the Vibrio species is due to the production of a 84-Kd enterotoxin which has a component (5B subunits) which binds to the mucosal ganglioside receptor (GM_1) and another component (A subunit) which enters the enterocyte and stimulates the secretion of water and electrolytes (secretory diarrhea). Pili (which help mucosal colonisation), mucinases (which counteract the protective effect of intestinal mucin) and neuraminidases (that favourably modify the ganglioside membrane receptor) are other virulence factors of the vibrio species.

Epidemiology Epidemics of cholera have been well known throughout the twentieth century. Since the 1960s, the seventh pandemic has been raging through the Indian subcontinent, especially in the Indo-Gangetic plains. Children below 5 years and subjects with the O blood group antigen are especially susceptible to cholera. Infants who are breast-fed and are less than two years of age are immune to cholera. Asymptomatic infections are 5 to 20 times more common than symptomatic illness in endemic areas. The attack rate has been estimated to be 2–6/1000/year in endemic areas like West Bengal. There is a wave of illness that often begins in the spring season. The disease is initially water-borne. There is a very high rate of intrafamilial spread as the affected individual often soils the house and utensils as he may be too weak to use a commode.

Clinical features The cardinal features of cholera are the acute onset of severe painless diarrhea and vomiting. As volume deficits approach 5 per cent, the subject feels weak, dizzy, thirsty and has postural hypotension and oliguria. With volume deficits of 10 per cent or more, the patient appears prostrate, drowsy, with sunken cheeks, sunken eyes and wrinkled skin[1] and has a rapid thready pulse with loss of skin turgor and severe hypotension even in the supine position. Severe weakness, muscle cramps and a hoarse voice are frequent accompanying clinical features. A milder illness may be indistinguishable from other causes of toxic diarrheas. The character of the stool has been described as resembling 'rice water'; motions are watery in consistency, grey-white in colour and sweet-smelling (not malodorous).

Diagnosis When cholera is suspected, a drop of the stool is placed on a slide within an area demarcated by plasticine and a cover slip placed on the slide. The slide is inverted (*hanging-drop preparation*) and subjected to dark-field micro

[1] and so called washer-person's hands

scopic examination. Motile curved rods are seen under the microscope in cholera. Immobilisation of the vibrio (in a stool specimen) by serogroup specific antisera is an alternative method of demonstrating the organisms but is not routinely available.

Laboratory tests are not routinely required for the management of a subject with cholera. When performed, these tests may reveal hemoconcentration, prerenal azotemia and metabolic acidosis with hypokalemia (with normal sodium concentration) of a varying degree.

Treatment The objectives of treating cholera include 1) the replacement of prior fluid deficits; 2) the replacement of ongoing fluid loss; 3) reducing the duration of diarrhea and fecal excretion of organisms with the use of appropriate antimicrobials; and 4) the institution of normal oral intake at the earliest possible time.

The basic principle of fluid replacement therapy is that in cholera the intestinal *glucose sodium cotransport*[1] system is intact; if salt is administered along with glucose in solution, both can be absorbed across the intestinal mucosa. Severe dehydration usually requires intravenous fluid administration. The average fluid deficits are 10 per cent of the body weight (5 litres in the 50 kg average adult). Approximately half of the estimated fluid deficits can be corrected over the first hour (1–2 ml/kg/min) and the rest administered over a further period of the three hours. Ongoing losses should be equal to stool volume.[2] Decrease in thirst, increase in the urinary output, the return of skin turgor to normal, return of pulse to normal strength and rate, all signify clinical improvement. The choice of a fluid for intravenous administration is guided by the isotonic loss of fluids in cholera. Ringer's lactate is the commercial fluid which has an electrolyte composition similar to diarrhea losses, and should be preferred[3] (Table 8.9). Plasma expanders or vasopressors should not be used as they do not correct the dyselectrolytemia that accompanies the volume deficit.

Mild or moderate dehydration can be treated with oral rehydration using *glucose electrolyte* solutions. WHO recommends a solution which contains 20 g glucose, 3.5 g sodium chloride, 2.9 g trisodium citrate (or 2.5 g of sodium bicarbonate) and 1.5 g of potassium chloride per litre of drinking water. A *rice oral rehydration solution* (rice ORS) which consists of 50 g rice instead of 20 g glucose has been shown to be better than the glucose-based ORS; it reduces

[1] Glucose-linked enhanced transmucosal transport of sodium

[2] In some endemic areas patients are managed on cholera beds made of foldable canvas and which have a central hole into which fits a sleeve to guide stools into a measuring bucket.

[3] Do not use 5% dextrose to replace fluids in diarrheal disease. Normal saline lacks potassium and bicarbonate.

Table 8.9 Electrolyte composition of cholera stool and alternatives for replacement therapy

Concentration (mmol/L)	*Cholera stool*	*WHO ORS*	*Normal saline*	*Ringer's lactate*
Sodium	135	90	154	131
Potassium	15	20	0	4
Chloride	100	80	154	111
Bicarbonate	45	30	0	26

Cholera stools in children contain less sodium, chloride and bicarbonate but more potassium.
The WHO solution refers to the bicarbonate form; an alternative citrate form is also available.

Table 8.10 Antimicrobial treatment of cholera

Drug	Dosage	
	Adults	Children
Tetracycline	500 mg q 6 hours for 72 hours	Avoid
Doxycycline	300 mg single dose	6 mg/kg single dose in children<15 yr
Furazolidone	100 mg q 6 hours	5 mg/kg/day in 4 divided doses
Erythromycin	250 mg q 6 hours	30 mg/kg/day in 4 divided doses
Trimethoprim-Sulfamethoxazole	5/25 mg/kg bid for 72 hours	Same as in adults

fluid stool losses by 30–40% more than the glucose-based alternative. Rice cereal provides oligosaccharides which provide the substrate for the facilitated cotransport of sodium. The rice ORS can be easily prepared by boiling 50 g of rice powder with a litre of water and adding 2–3 pinches of salt. The solution is allowed to cool and used within 8 hours of preparation.

Antimicrobial regimens which drastically reduce the intestinal content of vibrio are shown in the Table 8.10. The reduction of both the duration of diarrhea as well as its volume by 50 per cent, and the reduction of the fecal excretion of organisms to 2 days has been reported with all the regimens.

Natural course and complications Uncomplicated cholera is a self-limited disease of 2 to 5 days duration. Mortality rates are less than 1 per cent with prompt oral rehydration measures. Complications include acute renal failure, metabolic acidosis and superadded pneumonia (either due to aspiration or due to sepsis).

Prevention The prevention of cholera hinges on hygienic habits of the family members and the community. Using clean boiled water, the washing of hands with soap and water after defecation and appropriate disposal of soiled linen (bleaching powder is a good disinfectant) are important measures.

Campylobacter Infections

Microbiology *Campylobacter* are comma-shaped motile gram-negative bacilli which cause a spectrum of illnesses in humans, ranging from diarrhea to bacteremia. Three species of importance to humans are *C. jejuni, C. fetus* and *C. coli. C. fetus* is resistant to the action of serum components such as complement and hence can cause a bacteremic illness. The other two species cause an invasive enteritis predominantly affecting the small bowel (*C. jejuni*) and an invasive colitis affecting the large intestine (*C. coli*). A fourth species has been renamed *Helicobacter pylori.*

Epidemiology *C. fetus* primarily affects adults with diabetes or a malignancy, and causes a bacteremic illness—*systemic campylobacteriosis.* Males, and people over the age of 50 years are commonly affected and a large proportion of these subjects have worked with livestock (*Campylobacter* species are endemic in animals). *C. jejuni* is now recognised as the most common cause of bacterial diarrhea in several tropical countries. Asymptomatic gastrointestinal carriage is very common and children in the age group of 1–5 years are affected most often. Spread among household contacts is very common. Infection is also quite common in homosexual individuals and in patients with HIV infection. *C. coli* causes a diarrheal illness.

Clinical features

Systemic campylobacteriosis: Bacteremia without localising infection is the most common feature of this illness. Fever, chills, headache, non-productive cough and confusion are common. Colicky abdominal pain is common and a third of patients may have a diarrheal illness. Hepatosplenomegaly (of a mild degree) may acompany the clinical syndrome. Rare features of the bacteremic illness are endocarditis (10%), meningitis (10%) and thrombophlebitis at sites of venipuncture.

Campylobacter enteritis The illness typically begins with the abrupt onset of colicky periumbilical pain and profuse foul-smelling diarrhea. A dysenteric illness is seen in 30 per cent of patients. The illness is often self-limited, with recovery occurring within a week. Uncommon complications of diarrheal illness include acute appendicitis, bowel perforation and intussusception.

Postdiarrheal complications include a postinfectious reactive arthritis (in individuals with the HLA-B 27 haplotype), the hemolytic-uremic syndrome and the Guillain-Barre syndrome.

Diagnosis The diagnosis is established by isolating the organisms in blood cultures utilising specialised media (bacteremic illness) or by demonstrating the typical comma-shaped organism with a Gram stain of the stool specimen (diarrheal illness). The stools show a prominent leucocytosis, a feature common to several invasive enteropathogens.

Treament Enteritis due to Campylobacter species is self-limited and oral rehydration of the affected individuals is sufficient. Therapy of bacteremic illness is feasible with chloramphenicol or ampicillin.

Helicobacter Infections

Microbiology *Helicobacter pylori* (formerly called *Campylobacter pylori*) is a motile gram-negative rod which is uniquely adapted to a habitat within the stomach. It has been associated with antral gastritis, peptic ulcer disease and, perhaps, gastric cancer.

Epidemiology and pathogenesis Infection with *H. pylori* increases with age, and intrafamilial spread is common. *H. pylori* survives in the highly acid environment of the gastric antrum and also overlies the gastric-type cells of the duodenum. It secretes a cytotoxin injurious to the epithelial cells, and the gastric tissues becomes inflamed. Cytokines released as a consequence of this inflammation further aggravate the *antral gastritis* by increasing acid secretion; the inflamed gastric tissue is more susceptible to damage by acid.

Clinical features and diagnosis Acute infection with *H. pylori* is associated with epigastric pain. Chronic infection is associated with dyspeptic symptoms similar to those of chronic peptic ulcer disease.

The diagnosis of *H. pylori* infection can be made with an endoscopic biopsy which is subjected to culture and histologic examination.

Treatment *H. pylori* is susceptible to bismuth compounds (525 mg qid), metronidazole (250 mg tid) and amoxycillin (500 mg qid) given alone or in combination.

Escherichia coli Infections

Microbiology The natural habitat of E. coli organisms in humans is the gastrointestinal tract where they are the most numerous of the Enterobacteriaceae. Normally, E. coli causes disease in humans only when it is displaced from its usual habitat to other sites, such as the biliary tract, the urinary tract, or the subarachnoid space and the meninges. Certain strains of E. coli that are not normally part of the resident flora can cause diarrheal disease when introduced into the gastrointestinal tract. Diarrheagenic strains may be grouped as 1) enterotoxigenic (cholera-like), 2) enteroinvasive (Shigella-like),

3) enteroadherent (many but not all of these strains correspond to the classic enteropathogenic serotypes), 4) hemorrhagic colitis-producing strains, and 5) enteroaggregating strains. Urinary tract infections due to E. coli are discussed in the chapter on renal disease.

Epidemiology Enterotoxigenic E. coli organisms are ubiquitous in developing countries and are a major cause of diarrhea in children and in travellers (traveller's diarrhea). The disease is spread through contaminated food or water. Person to person spread is rare. Enteroinvasive strains account for less than five per cent of the diarrheal disease caused by E. coli and its epidemiology is less clear.

Pathogenesis

Enterotoxigenic: E. coli adhere to the mucosal surface of the proximal small bowel by means of pili termed *colonisation factors*. They then elaborate pathogenic toxins that cause clinical disease. Two types of E. coli enterotoxin have been positively identified: heat labile (LT) and heat stable (ST). LT is closely treated to cholera toxin, reacts with a GM_1 ganglioside receptor

Table 8.11 Comparison of gastrointestinal syndromes due to E. coli infection

Feature	*ETEC*	*EIEC*	*EPEC*	*EHEC*	*EAggEC*
Epidemiology	• infection common in developing countries • 2nd commonest cause of infantile diarrhea in India (after rota virus)	endemic in developing countries <5% of all infective diarrheas	affects only infants <6 months in developing countries	disease seen in developed countries	commonest cause of persistent infantile diarrhea in India
Microbiology/ Mechanism	elaborate a labile cholera-like toxin and a polypeptide heat-stable toxin	invasive like shigella species	• focal aggregation in tissue cultures forming microcolonies • efface mucosa	elaborates shiga-like toxin	aggregatory pattern in tissue culture ? mechanism of illness
Reservoir/ source	• humans • contaminated food	• humans • contaminated food	infant formula feed in nurseries	poorly cooked beef	?
Site of pathology	proximal small intestine, noninvasive	invasive disease of colon	small intestine, non-invasive	colitis	small intestine + colon
Incubation period	10–12 hours	10–18 hours	9–12 hours	12–60 hours	20–48 hours
Symptoms	watery diarrhea, midabdominal cramps; no fever; lasts <7 days.	watery diarrhea, may cause dysentery with fecal leucocytes	watery diarrhea, fever, illness lasts 3–7 days	bloody diarrhea without fecal leucocytes, no fever, vomiting may occur; illness lasts 2–15 days	acute followed by persistent diarrhea
Duration of fecal excretion	short	short	short	prolonged	short
Treatment	cotrimoxazole/ ciprofloxacin	cotrimoxazole/ ciprofloxacin	cotrimoxazole/ ciprofloxacin	?	?

ETEC = Enterotoxigenic E. coli, EIEC = Enteroinvasive E. coli, EPEC = Enteropathogenic E. coli, EHEC = Enterohemorrhagic E. coli, EAggEC = Enteroaggregatory E. coli

site on the surface of the epithelial cell resulting in the stimulation of cyclic adenosine monophosphate (cAMP). The action causes active secretion of chloride ion and blocks absorption of sodium ion, resulting in a secretory diarrhea. The ST toxin appears to react with the same GM_1 ganglioside receptor site but induces fluid secretion in the intestine by a mechanism involving activation of guanylate cyclase (instead of cAMP).

Enteropathogenic: E. coli penetrate the glycocalyx of the epithelial cells, disrupt the brush-border, and cause a blunting of the villi. Associated crypt hypertrophy, histiocytic infiltration of the lamina propria, and a decrease in brush-border enzymes are common.

Enteroinvasive: E. coli organisms produce disease that closely resembles shigellosis. The pathogenesis of hemorrhagic colitis caused by E. coli O157:H7 appears to be related to the production of a cytotoxin.

Clinical features The clinical features of the various syndromes are summarised in table 8.11.

Diagnosis E. coli diarrheal disease is diagnosed primarily on the basis of clinical and epidemiologic data. Laboratory diagnosis is difficult because diarrheagenic strains differ little morphologically or biochemically from those normally present in the intestine. Stool

Table 8.12 Clinical differentiation of infective small and large bowel diarrhea

Feature	*Location of infection*	
	Large bowel	*Small bowel*
Mechanism	Invasive, ulcerogenic pathogens	Non-invasive, enterotoxigenic pathogens
Organisms	EIEC, EHEC *Shigella* *Salmonella* *Campylobacter* *Entameba histolytica*	ETEC, EPEC, EAggEC *Vibrio cholerae* *Giardia lamblia* *Rotavirus*
Pain	Lower abdomen, rectal	Mid-abdomen, periumbilical
Associated symptoms	Tenesmus*	Borborygmi**
Stool volume	Small	Large
Stool consistency	Fecal, mucoid	Watery
Blood in stool	Common	Rare
Leucocytes in stool	Common, other than in amebiasis	Rare
Proctosigmoidoscopy	Mucosal ulcers, friable mucosa	Normal
Complications	Toxic megacolon Hemolytic uremic syndrome Reactive arthritis	Dehydration Dyselectrolytemia

* Tenesmus is the spasmodic contraction of the anal sphincter with pain and a persistent desire to empty the bowel with involuntary ineffectual straining efforts

** A gurgling splashing rumbling sound in the intestines–usually due to the passage of gas through the liquid intestinal contents

smears appear normal with enterotoxigenic and enteropathogenic strains but reveal 1) many polymorphonuclear leukocytes when disease is caused by enteroinvasive strains, and 2) red blood cells (without leukocytes) in infection with enterohemorrhagic strains. In general, the toxin producing E. coli causes small bowel diarrhea whereas invasive strains cause large bowel diarrhea (Table 8.12).

Management Fluid and electrolyte replacement is the cornerstone of therapy. Oral administration of a glucose-containing electrolyte solution is preferred. A single 100 mg daily dose of doxycycline prevents traveller's diarrhea for upto three weeks. One double-strength tablet of trimethoprim-sulfamethoxazole (160 mg of trimethoprim and 800 mg of sulfamethoxazole), given twice a day for five days, effectively shortens the duration of diarrhea as do some of the fluoroquinolones (ciprofloxacin and norfloxacin).

Infection due to Pseudomonas Species

Mircobiology The pseudomonas species are obligate aerobic, motile, gram-negative rods. Pseudomonas aeruginosa is the most common species which infects humans. Most strains produce two pigments, pyocyanin (blue) and fluorescein (green). The organism produces several virulence factors, including an exotoxin, an elastase and a collagenase.

Epidemiology The pseudomonas species does not normally cause infections in healthy individuals. The organism can be occasionally found as commensals on the axillary and anogenital skin, especially among hospitalised patients. Pseudomonas survives in urinary receptacles and even in antiseptic solutions. Immunosuppressed patients (leukemia patients or those with organ transplants) or patients with impaired defense mechanisms due to breach of intact skin (burns) are especially vulnerable.

Clinical features The clinical features vary depending on the site of the infection. Otitis externa with purulent drainage is seen in diabetics, and is common in developing countries (even in the absence of diabetes). The disease is especially virulent in diabetics, in whom there may be mutilation of the ear or associated cranial nerve palsies. Ocular infection results in corneal ulceration and has been associated with the use of contact lenses (presumably due to contamination of the cleaning fluid). Pulmonary and urinary tract infections occur due to the contamination of respiratory therapy equipment or urinary catheters. Osteomyelitis is uncommon and is associated with open fractures. Among patients with burns, the region below the eschar is infiltrated initially.

Pseudomonas bacteremia can result in patients with burns or in a immunosuppressed state. The presentation is similar to that of gram-negative sepsis. The possibility of Pseudomonas as the etiologic agent of sepsis is suggested by two features: 1) the skin lesion of *ecthyma gangrenosum,* an indurated purple-black area with central ulceration and peripheral erythema found typically in the axillary or the anogenital region, and 2) the passage of green-coloured urine (a rare feature, presumably related to the hemoglobin pigment verdoglobin).

Diagnosis The diagnosis requires culture of the organism from secretions or from the blood.

Treatment Localised infections (such as otitis externa) can be treated with topical agents such as polymyxin B or colistin. Debridement of the necrotic area is important. Parenteral treatment with an antipseudomonal aminoglycoside (tobramycin 5 mg/kg/day; amikacin 15 mg/kg/day (in cases of resistance)) or an antipseudomonal penicillin (ticarcillin or piperacillin) is required for systemic infections. Serious infections can be treated with a combination of the two groups of agents or with the use of a third-generation cephalosporin (ceftazidine)

along with an aminoglycoside. An oral agent like ciprofloxacin is preferred for the treatment of urinary tract infection and osteomyelitis.

Plague

Plague is a zoonotic infectious disease caused by *Yersinia pestis,* a bacterium carried by rodents and transmitted by fleas. It is characterised either by generalised lymphadenopathy (*bubonic form*) or a pneumonitis syndrome (*pneumonic form of disease*).

Pathogenesis Plague is acquired by humans as a result of the bite of the rodent flea (*Xenopsylla cheopis*). They can also acquire the disease by handling infected animals or by exposure to respiratory droplets from persons or animals with the pneumonic form of the disease. The organism proliferates in the regional lymph nodes draining the area of the bite, resulting in regional lymphadenitis (bubonic form of disease). The architecture of the affected lymph node is destroyed, with infiltration by neutrophils and red cells, and thrombosis of local blood vessels. Secondary dissemination to the rest of the body occurs through the blood stream. Secondary involvement of the lungs is seen in the pneumonic form of the disease.

Epidemiology Plague (also called *black death*) has been known to humans for centuries. In fact, India was one of the countries most affected by the pandemic which raged through the latter half of the nineteenth century. More recently, plague has been brought to the attention of the medical community following the recent outbreak of disease in India. In August 1994, an outbreak of the bubonic disease was reported from the Beed district of Maharashtra, a known plague-*enzootic*[1] area. In late September of the same year, an explosive epidemic of pneumonic plague was reported in the city of Surat in adjoining Gujarat. By early October 1994, about 6,000 suspected cases had been reported from 12 states, with serologic confirmation (unvalidated) in about 700 people. Epidemiologists believe that an epizootic occurred in wild rodents in the preceding years and spilt over to commensal rodents in Maharashtra. This accounted for the primary cases of bubonic plague. The secondary cases of pneumonic plague probably resulted from the subsequent importation of the organisms, presumably by travellers into Surat (a port city with a large population of migrant workers).

Clinical features After an incubation period of 2–8 days after the bite of the flea, the patient develops chills, fever and malaise. About the same time (or within a few hours) she also notices intense pain and swelling (*buboes*) in the regional lymph nodes (usually the inguinal nodes). The buboes are oval swellings of variable size which are very tender and the overlying skin may be warm.

Pneumonic plague presents with cough, chest pain and often, hemoptysis; all these features occur in the setting of fever and lymphadenopathy. The sputum is purulent and laden with bacilli. When the bacteremic load is very heavy, the term *septicemic plague* is used.[2]

Whatever be the form of plague, the patient appears toxic and is prostrate with a moderate elevation of body temperature. Skin lesions are unusual, although there are reports of pustular lesions near the bubo, and of disseminated purpuric-necrotic lesions (hence the name black death). Because of extreme peripheral vasodilation, systemic blood pressure may be low. The liver and spleen also become palpable.

Investigations and diagnosis The peripheral blood counts are elevated with a polymorphonuclear leucocytosis of 10,000–20,000/mm^3, with a shift to the left. Evidence of the state of disseminated intravascular coagulation may be seen with thrombocytopenia and elevated fibrin

[1] Enzootic refers to an infection 'endemic' in animal vector, epizootic refers to an 'epidemic' of disease in the animal vector.

[2] The term is misleading ås plague is always associated with septicemia.

degradation products. Liver function tests are frequently abnormal. Renal functions may be deranged in the hypotensive patients.

The diagnosis of bubonic plague is clear when localised lymphadenopathy is associated with a sudden onset of severe prostration and pyrexia *without a history of any prior genital lesion.* In order to confirm the diagnosis, the bubo can be aspirated with a 20 gauge needle.[1] The aspirate is stained with Gram's or Wayson's stain: Y. pestis appears as a light blue bacillus with dark blue polar bodies with the latter stain. For confirming the diagnosis of pneumonic plague, the sputum must be stained similarly. The chest X-ray in pneumonic plague reveals broncho-pneumonia. Blood, sputum and the bubo aspirate may also be cultured for bacteriologic confirmation of plague. A passive hemagglutination test is also available for providing serologic confirmation.

Management Untreated plague has a mortality exceeding 50 per cent. Streptomycin is the treatment of choice. The drug is administered at a daily dose of 30 mg/kg (intramuscular, divided into two doses) for 10 days. Oral tetracycline (500 mg 6 hourly) is an effective alternative in adults and non-pregnant women. All patients should also be provided supportive care which includes proper hydration, nutrition and maintenance of an adequate blood pressure.

Prevention Plague is a preventable illness. The public should be educated about the need to prevent the access of rodents to food. Proper disposal of food, garbage and refuse is a complementary measure. Rodent control programmes must be implemented in warehouses, and docks; fumigation to destroy fleas must be combined with the use of rodenticides. Rodent burrows should also be sprayed with flea insecticides.

[1] The needle is filled with 1 ml saline and the bubo is aspirated till the saline becomes blood-tinged. If no fluid is aspirated, the saline may be injected into the bubo and reaspirated.

In the case of epidemics, the WHO should be notified within 24 hours. Attempts must be made to mitigate public hysteria through educational press and media releases. All close contacts of confirmed cases should be provided with chemoprophylaxis (tetracycline 15–30 mg/kg/day in 4 doses for 7 days). Contacts who refuse prophylaxis must be placed under medical surveillance. Patients with confirmed pneumonic plague must be placed under isolation for 3 days after starting treatment.

Other infections due to gram-negative bacilli and spirochaetes are summarised in Table 8.13.

ANEROBIC INFECTIONS

Anerobes are microorganisms which are unable to replicate in the presence of oxygen. This extreme oxygen sensitivity is partly due to their lack of the enzyme superoxide dismutase, which normally protects bacteria from the lethal effects of the superoxide radical. Anerobic bacteria vary widely in their sensitivity to oxygen. *Strict* anerobes grow best at an oxygen tension of less than 0.5 per cent. Most of the more pathogenic organisms are only *moderate* anerobes; these bacteria grow best at an oxygen tension of less than 3 per cent.

Pathogenesis Anerobic bacteria dominate the indigenous microbial flora of healthy persons. Anerobes outnumber aerobic and facultative bacteria in the colon by a ratio of 1000 to 1. On the skin, in the oral cavity and in the female genital tract, anerobes outnumber aerobes 10 to 1. Most anerobic infections are, therefore, *endogenous* in origin. Anerobic infections depend on a primary insult to the patient's defence mechanisms. Anerobes are often associated with ischemic, necrotic tissues, with the presence of foreign bodies, and with abscess formation; these environments have a *lowered oxidation-reduction potential* and permit spore germination and bacterial multiplication. A reduced environment also impairs the bactericidal activity of polymorphonuclear leukocytes, inhibits lymphocyte proliferation

Table 8.13 Less common infections of adults due to gram-negative bacilli and Spirochaetes

Disease	*Etiology*	*Epidemiology*	*Symptoms*	*Diagnostic tests*	*Treatment*
Gram-negative bacterial infections					
Group: Klebsiella, Enterobacter, Serratia	Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens	nosocomial infection, obstructed urinary tract predisposes, biliary tract, pneumonia	nosocomial pneumonia (in Klebsiella: uncommon features: 'red currant jelly' sputum, 'bulging fissure' on chest X-ray)	Gram-stain of sputum, exudate	*Klebsiella:* antipseudomonal aminoglycosides/ third-generation cephalosporins; *Serratia:* amikacin, third-generation cephalosporin, imipenem; *Enterobacter:* imipenem or antipseudomonal penicillin/ aminoglycoside
Group: Proteus, Providens, Morganella	Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii	normal fecal flora, infect wounds, ears, urinary tract	infect burns, otitis media, urinary tract infection	culture from blood, urine, exudate	*Proteus mirabilis:* ampicillin; *Proteus, vulgaris:* third-generation cephalosporin; *Providens:* amikacin or ciprofloxacin; *Morganella:* imipenem, third-generation cephalosporin
Brucellosis	Brucella abortus, B.melitensis, B. suis	occupational and rural disease of farmers, live-stock producers; acquired by ingesting infected milk of goat, cow or sheep	fever, prostration, muscular pain, back pain; hepatosplenomegaly of a mild degree; arthritis; **complications:** orchitis, endocarditis, bone lesions, cholecystitis, meningoencephalitis	blood cultures, serology (IgG agglutinins)	Doxycycline 100 mg oral bid for 3–6 wks plus Streptomycin 1 g im daily for 14 days children < 8 yrs: substitute rifampicin for doxycycline

Table 8.13 Less common infections of adults due to gram-negative bacilli and Spirochaetes (contd.)

Disease	*Etiology*	*Epidemiology*	*Symptoms*	*Diagnostic tests*	*Treatment*
Legionnaire's disease	Legionella pneumophila	airborne, airconditioner vents, hot water distribution systems implicated	headache, fever, pneumonitis, gastrointestinal symptoms (diarrhea), serology	culture requires special media, immunofluorescent stain of sputum	Erythromycin 0.5-1 g i.v./oral for 14 days
Yersiniosis	Yersinia enterocolitica (gastrointestinal disease), Yersinia pseudotuberculosis (systemic disease)	feco-oral transmission	Y. enterocolitica: diarrhea due to enterotoxin; erythema nodosum; monarthritis after illness in HLA-B27+ individuals. Y.pseudotuberculosis: enterocolitis with prominent involvement of mesenteric lymph nodes, appendicitis-like syndrome	isolation of bacilli from stools, serology	Symptomatic treatment of diarrheal disease; Norfloxacin, ampicillin for Y.pseudotuberculosis
Bartonellosis (Carrion's disease)	Bartonella bacilliformis	transmitted by sandfly Phlebotomus; humans are the sole reservoir. Seen only in S. America	• **Oroya fever:** the initial febrile phase, pain in joints and bones, anemia, lymphadenopathy • **Verruga peruana:** eruptive phase that develops weeks later with hemangioma-like papules	Intraerythrocytic organisms seen	Chloramphenicol 2–4 g/day for 7 days
Rat-bite fever	1. Streptobacillus moniliformis 2. Spirillum minus (a spirochaete)	rodent bite	relapsing fever, rash polyarthralgia or arthritis (more with the first agent), regional lymphadenopathy	S. moniliformis may be cultured from blood S. minus can be seen in blood films on dark field illumination	For both agents: Procaine penicillin 1.2 million u/d for 7 days

Table 8.13 Less common infections of adults due to gram-negative bacilli and Spirochaetes (contd.)

Disease	*Etiology*	*Epidemiology*	*Symptoms*	*Diagnostic tests*	*Treatment*
Tularemia	Francisella tularensis	occupational disease of farmers, butchers and fur-handlers; transmission by blood-sucking arthropods	• **ulceroglandular** (90%): local papule on finger that ulcerates, regional lymphadenopathy; fever, prostration • **typhoidal** (5%): fever, abdominal pain • **oculoglandular** (3%): eye infection with regional lymph node enlargement • **glandular** (2%): cervical lymphadenopathy without primary lesion	recovery of organism from lesion, lymph node or blood	Streptomycin 0.5 g im q 12 hrs till afebrile followed by 0.5 g i.m. od; 2% homatropine for ocular involvement
Melioidosis	Pseudomonas pseudomallei	endemic in SE Asia; animals are reservoirs; contact with contaminated water or air-borne material	symptoms like typhoid or tuberculosis; necrotising pneumonia; cavities+; upper abdominal colic; fever, diarrhea	isolation of microbe from sputum or blood cultures; serology	**mild disease:** trimethoprim / sulfamethoxazole 20 mg/ 100 mg/kg/d for 30 days **severe illness:** iv ceftazidime (if available) 30 mg/kg q 6 hrs iv for 14 days followed by above regimen
Glanders	Pseudomonas mallei	microbe found in horses, mules and monkeys; humans infected rarely	symptoms like melioidosis	isolate microbe from blood or discharge	not certain; regimens as for melioidosis have been used with success

Table 8.13 Less common infections of adults due to gram-negative bacilli and Spirochaetes (contd.)

Disease	*Etiology*	*Epidemiology*	*Symptoms*	*Diagnostic tests*	*Treatment*
Spirochaetal infection					
Leptospirosis (Weil's disease)	Leptospira icterohemorrhagica	contact with urine of infected animals	fever, chills, myalgia, jaundice (usually by day 5), hemolytic anemia, renal involvement, myocarditis	blood cultures (first 10 d), dark field microscopy, agglutination titres (after day 7)	only if within 4 days of onset, doxycyline 100 mg twice daily for 7 days
Lyme disease	Borrelia burgdorferi	bite of the Ixodid tick	Stage1: migrating erythematous rash (erythema chronicum migrans), fever, neck stiffness; Stage 2: weeks to months later, meningitis cranial nerve palsies, chorea, peripheral neuritis, cardiac AV block; Stage 3: weeks–2 years, arthritis	increased IgG antibodies after 2–3 weeks	**Early:** doxycycline (100 mg bd) or amoxicillin (500 mg tid) or tetracycline (250 mg qid) or oral penicillin (500 mg qid) for 10-20 days **Late (CNS/cardiac):** ceftriaxone (2 grams i.v./d) or Penicillin G (20 million u/day) for 14 days
Yaws	Treponema pertenue	direct contact, common in developing countries	constitutional symptoms with papular eruption, later destructive lesions of skin and bones	dark field microscopy, serology for syphilis positive	Benzathine penicillin G 2.4 million units i.m.
Pinta	Treponema carateum	direct contact, common in developing countries	scaling papular eruption on hands, legs, feet, lymphadenopathy; maculopapular rash after 4–12 months	dark field microscopy, serology for syphilis positive	Benzathine penicillin G 2.4 million units i.m.

Many anerobes can produce *enzymes* (such as collagenase, hyaluronidase) that may cause tissue damage. Many *Bacteroides* species produce a heparinase that may account for their propensity to produce vascular thrombosis. Anerobic bacteria can also produce *endotoxins.* The virulence of the *Clostridium* species depends on the production of various *exotoxins. Clostridium perfringens* produces toxins that may cause massive tissue necrosis over a very short period.

Clinical features Anerobic infections frequently involve multiple bacterial species, that is, they are *polymicrobial;* aerobic or facultative organisms are present together with anerobes. These infections are an example of microbial synergism; the aerobic bacteria consume oxygen and thereby provide a reduced environment in which the anerobes can multiply. Aspiration pneumonias, lung abscesses, empyemas, intraabdominal abscesses, pelvic infections, and certain necrotising infections of the skin and subcutaneous tissue are some examples of polymicrobial infections. A number of other clues should lead the clinician to suspect anerobic infection. Anerobic infections frequently produce progressive tissue necrosis and the organisms burrow through tissue planes. The *presence of gas* in tissues should always raise the question of anerobic infection because many anerobes are gas producers. A *foul smell* is frequently associated with anerobic infections particularly when Bacteroides species are present. *Septic thrombophlebitis* may be a feature of anerobic infections, especially those caused by *Bacteroides fragilis. Negative aerobic cultures* may also indicate the presence of anerobic infection, although it may also signify the presence of mycobacteria or fungi. Finally, if there is a *lack of response to therapy* appropriate for aerobic or facultative organisms, the possibility of an anerobic etiology should always be considered.

Laboratory diagnosis A simple Gram-stain often provides the most rapid clue to the etiologic diagnosis since many anerobes have a characteristic morphologic appearance. Careful collection of the specimen, immediate transport in an appropriate environment and special processing are all essential if an anerobic infection is suspected. Since anerobes constitute most of the normal microbial flora of humans, specimens that have passed through the oropharynx, intestinal tract, or the genital tract will inevitably be contaminated and are therefore useless; sputum, throat swabs, bronchoscopic washings, cervical or vaginal swabs, voided urine, and stool specimens are unsuitable. The most useful specimens are either direct aspirates of closed-space infections or specimens from body fluids or tissues that are normally sterile. For instance, transtracheal or percutaneous lung aspirates are used to evaluate suspected anerobic pulmonary infections. Direct aspirates of abscesses or of deep tissue infections, surgical specimens, and blood are other specimens which are suitable for anerobic culture. Aspirated fluids in sealed syringes are preferable to swabs. It is essential to transport specimens to the microbiology laboratory rapidly. When any delay is anticipated or when the use of swabs is unavoidable, special anerobic transport media should be employed.

Specific anerobic infections Although anerobic bacteria can cause a wide variety of infections, there are certain clinical syndromes that typically involve anerobes. It is often customary to classify anerobic infections into those above the diaphragm (head, neck and chest) and those below the diaphragm (intraabdominal) as the microbial spectrum at the two sites is different. *Peptostreptococci, Bacteroides* species, and *fusobacteria* are common anerobes in the oral cavity. These organisms are implicated in anerobic infections of the head and neck. Examples include *Vincent's angina* (trench mouth), *Ludwig's*

angina (submandibular cellulitis), *peritonsillar abscesses* and periodontal disease. These anerobic bacteria can also invade the lung parenchyma after aspiration; the extensive tissue necrosis that results can cause *pneumonitis* (aspiration pneumonia), a *lung abscess*, and, occasionally, an *empyema.* Anerobic bacteremia can lead to multiple visceral abscesses. Although anerobic bacteremia accounts for only a small percentage (< 3 per cent) of all significant bacteremias, it can lead to *endocarditis.* Bacteroides species account for the majority of clinically significant anerobic bacteremias. In the central nervous system, anerobes are extremely important in the pathogenesis of *brain abscesses.* The mixed microbial flora responsible for brain abscesses reflect the origin of many of these abscesses by direct extension from foci of chronic infection in the mastoids, paranasal sinuses, or the middle ear. Anerobes responsible for *infections below the diaphragm* are of *enteric origin*; they differ from the oropharyngeal anerobes. The colon is laden with anerobic bacteria, *Bacteroides fragilis* being the most numerous. Other enteric anerobes include *clostridial species, peptococci,* and *peptostreptococci.* Anerobes are often implicated in *intraabdominal infections* such as diverticular and appendiceal abscesses, peritonitis, and postoperative infections; aerobic or facultative organisms (such as Escherichia coli, Klebsiella, Proteus, and Enterococci) are also frequently present. Anerobic organisms are also frequently found in pyogenic liver abscesses. The female genital tract, the vagina and cervix harbour the same range of anerobic bacteria as is found in the lower gastrointestinal tract. Anerobes appear to combine with aerobes (such as Gardenella vaginalis) to produce *non-specific vaginitis* (also called bacterial vaginosis). Anerobic bacteria are also frequently implicated in non-gonococcal infections of the female genital tract, including vulvovaginal, and Bartholin's gland abscesses, endometritis, salpingitis, tubo-ovarian abscesses, and pelvic peritonitis. Anerobic bacteria can also cause infections after gynecologic surgery, after parturition, and following abortions. Clostridal myometritis with septicemia is a particularly dangerous complication of septic abortions.

Anerobic infections of the skin and soft tissues are rare. Multiple aerobic and anerobic organisms can cause synergistic skin infections such as *Meleney's progressive synergistic gangrene* (granulating ulcer due to combined infection with Staph. aureus), necrotising fasciitis, and *Fournier's gangrene* (involving the perineum). Anerobes are also frequently recovered from cutaneous abscesses and ulcers.

Therapy Despite important advances in antibiotic therapy for anerobic infections, surgical treatment is often required when anerobic infections have burrowed deeply into tissue planes.

Generally, oral anerobes are sensitive to penicillin (except a few strains of B. melaninogenicus). In contrast, B. fragilis of *enteric* origin is resistant to penicillin. Among other enteric anerobes, C. perfringens isolates are usually penicillin sensitive. As a result of this spectrum of activity, penicillin is the drug of choice for most clostridial infections but is not effective against abdominal or pelvic infections caused by B. fragilis.

Clindamycin has excellent activity against most oral and enteric anerobes, including B. fragilis. Together with chloramphenicol, clindamycin has been accepted as one of the drugs of choice for treating B. fragilis infections and is an alternative to penicillin in infections caused by anerobes of oral origin. Chloramphenicol is active against most anerobic bacteria, including B. fragilis. Metronidazole has emerged as a major drug for the treatment of anerobic infections although its antimicrobial activity is limited to anerobes such as Fusobacterium species, C. perfringens, and most Bacteroides species (including B. fragilis).

Clostridial Infections

Clostridia are gram-positive anerobic spore-forming bacilli which are found in the lower gastrointestinal tract and in the soil. Three major groups have been described: *histotoxic* species (C. perfringens, C. novyi, C. septicum, C. bifementans), *enterotoxigenic* species (C. perfringens and C. difficile), and *neurotoxic* species (C. tetani and C. botulinum). Clostridia are pathogenic by virtue of elaborating potent exotoxins. For example, C. perfringens produces an α-toxin which is a lecithinase and has hemolytic and necrotising properties. The exotoxin of C. tetani is discussed under tetanus.

Clostridial wound infections

C. perfringens is the species most frequently responsible for wound infections. Although contamination of wounds with clostridia is a fairly common event, the development of a gas-forming wound infection is distinctly uncommon. This is because a lowered oxidation-reduction potential is required for the clostridial spores to germinate and produce the pathogenic exotoxin. The presence of devitalised tissue, an impairment of blood supply to the tissue, or the presence of foreign bodies within the wound predispose to a low oxidation-reduction potential and, therefore, to clostridial infection.

Clinical features

Clostridial anerobic cellulitis: Anerobic cellulitis is a gas-forming infection of the skin and subcutaneous tissues. The muscle is not invaded. The skin overlying the wound is not painful but telltale crepitus is detected. The wound discharges a dark, grey-brown, foul-smelling exudate. When the infection occurs in a loculated wound cavity, the term *Welch abscess* is used. A Gram-stain of the exudate reveals the characteristic plump, gram-positive bacilli.

Clostridial myonecrosis (gas gangrene): Gas gangrene is usually the consequence of a traumatic injury or penetrating wounds or the result of a surgical procedure on the colon or biliary tract. Symptoms begin about 1 to 4 days after the wound or surgery. There is severe pain at the site of injury associated with fever, malaise and tachycardia. On examination, the skin overlying the involved area is discoloured and there is marked tenderness and crepitus on palpation. The exudate is serosanguinous and has a 'sweet' smell.

The diagnosis is established by radiographic studies demonstrating gas in the muscles and in the subcutaneous tissues, typically crossing interfascial planes.

Management When left untreated the mortality of gas gangrene is about 20–30 per cent. Prompt surgery is, therfore, essential to define the extent of the wound infection and to excise all infected and devitalised tissue. Surgical debridement involves exposing and removing the affected muscle that appears pale red, fails to contract with stimulation and does not bleed when cut. Penicillin G (10 to 40 million u/day i.v. in divided doses) for two weeks is the drug of choice. Alternative drugs include intravenous metronidazole (2 g/day), chloramphenicol (2 g/day) or clindamycin (1.8 g/day). The role of intravenous polyvalent equine antitoxin or hyperbaric oxygen therapy is not clear and their use is not recommended.

Enteric clostridial infections

Clostridial food poisoning: The features of bacterial food poisoning syndromes, including those due to Clostridium perfringens are summarised in Table 8.14.

Pseudomembranous enterocolitis: Also called antibiotic-associated colitis, this disease is due to toxin-forming strains of *Clostridium difficile.* Almost any antibiotic (with the exception of streptomycin and vancomycin) can cause pseudomembranous colitis, especially when used for a prolonged time (upto 4 weeks). The disease begins as florid, watery diarrhea associated with abdominal cramps and fever. A physical examination reveals abdominal tenderness.

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Table 8.14 Differential diagnosis of bacterial food poisoning

	Incubation period					
	<6 hours		*6–12 hours*	*>12 hours*		
Organism	Staph. aureus	Bacillus cereus	C. perfringens	Salmonella	V. para hemolyticus	C. botulinum
Source	uncooked dairy food, sliced meat	fried rice	cooked meat	contaminated meat/dairy product	seafood	canned food
Clinical features	vomiting, no fever	vomiting, abdominal pain, diarrhea	abdominal pain, diarrhea	fever, abdominal pain, diarrhea	vomiting, diarrhea	vomiting, cranial nerve palsies, motor weakness

The diagnosis is clinically suspected in a subject on antibiotics for some other indication who develops severe diarrhea. The stools show leucocytes. Definitive confirmation requires performing assays for the toxin in stool specimens. Treatment consists of discontinuing the offending antibiotic and instituting vancomycin (125 mg qid for 7–10 days).

Tetanus

Tetanus is an infective, neurotoxic disease caused by toxins elaborated by *Clostridium tetani* and characterised by severe, intermittent tonic spasms of the voluntary muscles.

Pathogenesis *Clostridium tetani* is a motile, gram-positive, anerobic, spore-forming bacillus which can be found in the soil and in animal feces. The organism produces an exotoxin called *tetanospasmin* which is absorbed from local nerve endings at the portal of entry and carried to the anterior horn cells of the spinal cord. The toxin binds to the ganglioside membrane of inhibitory synaptic neurons, blocking the release of inhibitory transmitters. The result is motor hyperactivity causing a generalised tonic spasticity, usually punctuated by intermittent tonic convulsions. The toxin can also reach the brainstem through the blood-stream and cause a 'descending' pattern of tetanus with prominent involvement of the masseters and facial muscles.

Epidemiology Tetanus is usually acquired when wounds are contaminated with infected soil containing bacterial spores. It is particularly common in the tropics where the soil is manured and people often walk barefoot. Certain wounds are more '*tetanus-prone*' than others. Such wounds are often more than 6 hours old, are stellate in configuration, are more than 1 cm deep, have devitalised tissue or are contaminated (on simple visual inspection). Crush injuries, missile hits and burns are tetanus-prone injuries. Linear, fresh (<6 hours), superficial (<1 cm deep) wounds which are due to cuts with clean surfaces (knives or glass) are examples of 'non-tetanus-prone' wounds.

Tetanus neonatorum refers to a similar illness in neonates when the umbilical cord is severed or dressed with contaminated instruments. Septic abortion can also be complicated by tetanus if the instruments are contaminated with spores. The organism itself is a contaminant in crude heroin and can cause disease in drug addicts when injected subcutaneously. Another variant seen in developing countries is *cephalic* tetanus which is associated with trauma to the face or neck and is characterised by cranial nerve palsies. An example is *otogenic* tetanus which

occurs in children with chronic otitis media; clostridia are introduced into the middle ear when a dirty cloth or foreign object (such as a hair pin) is used to remove ear discharge. If untreated, cephalic tetanus can progress to generalised tetanus. Rarely, tetanus may be *localised* and manifest as spasticity limited to a group of muscles near the wound.

Clinical features Symptoms of tetanus usually begin after an incubation period of 8–12 days (range 3–50 days), when the initial injury may have healed. Sometimes the injury may be so innocuous (such as a thorn prick) that the patient may not recollect it unless specifically asked. Premonitory symptoms include stiffness, twitching and irritability of the muscles near the wound (especially the flexors). This is followed by clear-cut muscular spasms, initially involving the masseters and muscles of mastication, followed in sequence by the muscles of the back of the neck and finally progressing to involve the abdominal muscles (recti), the back and limb musculature. The spasms occur in paroxysms but the relaxation of muscles between spasms is not complete. Spasms are often provoked by movements or sudden noise. The tonic spasms of the muscles produce a typical posturing and appearance: *trismus* results from spasm of the masseters (hence the name *lockjaw*), a sardonic facial expression with a fixed smile and raised eyebrows is seen due to a spasm of facial muscles (*risus sardonicus*), head retraction may occur with extension of the spine (*opisthotonus*). Spasm of the external sphincters may result in urinary retention or constipation. Dysphagia may interfere with nutrition and laryngeal muscle spasms can interfere with respiration. There is usually associated autonomic hyperactivity, manifesting as excessive sweating, fluctuating hypertension, and periodic tachycardia. Fever, if present, is only mild and the *sensorium is usually clear in the presence of widespread spasms.*

If untreated, a few cases improve spontaneously, with the paroxysms diminishing over several weeks. In other cases complications (such as bronchopneumonia, asphyxia, fractures of the spine) supervene and death results, usually within a week.

Diagnosis A history of a contaminated wound in a non-immune person, prominent spasms with a typical pattern of muscular rigidity, and an intact sensorium help differentiate tetanus from meningoencephalitis. Strychnine poisoning can mimic tetanus but there is no fever, relaxation is complete between spasms, and the neck and jaw muscles are involved infrequently in spasms. Phenothiazine drugs can produce tetanus-like rigidity but other signs of basal ganglia dysfunction are usually apparent. A history of dog bite and prominent laryngeal spasms point to the possibility of rabies. Local causes of trismus (peritonsillar or retropharyngeal abscess) are usually evident from the history and physical examination.

Management The basic principles of management include ensuring a patent adequate airway, the early use of immune serum globulin, control of spasms, local care of the wound and nursing care to prevent potential complications.

A tracheostomy may have to be performed if laryngeal spasms are severe. Mechanical ventilation may also become essential if neuromuscular blockade is required to control spasms (see below). Gastric intubation for feeding should be considered to ensure adequate nutrition; intravenous hyperalimentation is preferable, if available, as it avoids the hazard of aspiration. Urinary catheterisation is indicated if there is urinary retention. Chest physiotherapy and frequent turning of position are important adjunctive measures.

The use of tetanus immunoglobulin neutralises 'non-fixed' toxin and prevents further toxin production, but has little effect on 'fixed' toxin. A single intramuscular injection of human tetanus immunoglobulin (of 3000 units) is recommended in cases of established tetanus.

The use of equine antiserum is to be discouraged because of the potential for hypersensitivity reactions; if human antiserum is not available, 50,000 units of equine antiserum may be used (i.m. or i.v.). Intrathecal injection of the antiserum is not recommended.

Muscle spasms are controlled with benzodiazepines, chlorpromazine or short-acting barbiturates. Diazepam is the drug of choice for controlling seizures, spasms and for sedation. Whereas 5–10 mg given orally every 2–4 hours is sufficient for mild cases, severe cases often require intravenous administration of 10–20 mg every 3 hours (maximum of 3 mg/kg over 24 hours). Neuromuscular blockade with a curariform agent (pancuronium bromide) may be required but must be preceded by mechanical ventilation. There are also reports of pyridoxine being beneficial in neonatal tetanus.

Local debridement of the wound is also important. However, the value of antibiotics is doubtful. They are used for ensuring wound asepsis and for eradicating residual cells of C. tetani that could produce more toxin. Penicillin G (2 million units i.v. 6 hourly) or tetracycline (500 mg i.v. 6 hourly) given for 10 days eliminate residual bacilli in the wound.

Tetanus is a preventable disease. Routine immunisation of children and adults is recommended. A minimum of three doses of tetanus toxoid (separated by 6 weeks) are recommended, followed by booster doses every 5 years. Since tetanus does not provide lasting immunity, cases with established tetanus must also be immunised. The prophylactic use of antiserum in tetanus-prone wounds is recommended. Table 8.15 summarises the indications for the use of tetanus toxoid and antiserum when managing an adult with a wound.

Botulism

Botulism is a neurotoxic disease caused by Clostridium botulinum, which is characterised by the acute onset of symmetric pure motor paralysis, typically involving the bulbar and limb musculature. C. botulinum produces at least three different neurotoxins (potency-wise A>B>E).

Pathogenesis Botulism usually occurs due to contamination of food with spores of C. botulinum. Occasionally, wounds contaminated with spores can also result in illness (wound botulism).

Clinical features Typically, botulism begins as an acute neurologic illness which starts about 12–36 hours after ingestion of contaminated food. Fever is usually absent. Evidence of bulbar dysfunction is prominent with ptosis, pupillary

Table 8.15 Tetanus prophylaxis and immunisation

History of tetanus immunisation	*Immunisation schedule*			
	Tetanus-prone wound		*Non-tetanus prone wound*	
	Tetanus toxoid	Antiserum	Tetanus toxoid	Antiserum
unknown or <3 doses or>3 doses but no boosters in the last 5 years	yes	yes	yes	no
3 or more doses within last 5 years	no	no	no	no

abnormalities, extraocular muscle paresis, swallowing difficulties and dysarthria. Neurologic findings are symmetrical. There may be a descending pure motor paralysis involving the musculature of the trunk and extremities. Conversely, botulism may also evolve as an ascending paralysis with bulbar dysfunction following weakness of the extremities. Respiratory muscle weakness is a potentially life-threatening complication. The visceral muscles are also affected, with constipation, ileus (bowel muscle paralysis) and urinary retention (bladder muscle weakness) being prominent features.

Diagnosis The diagnosis requires demonstrating the toxin in food, stools or blood.

Management Treatment consists of supportive care (which involves careful monitoring of the need for respiratory assistance) and administration of polyvalent ABE equine antiserum (after a test dose to exclude hypersensitivity).

MYCOBACTERIAL INFECTIONS

Tuberculosis

The term tuberculosis refers to a clinical disease caused by *Mycobacterium tuberculosis*. Tuberculous infection may occur without the disease but the term tuberculosis is not used for such infections.

Epidemiology

Transmission of disease: Transmission of *M. tuberculosis* is through aerosol particles which measure 5–10 μm in size (and contain 2 to 3 bacilli) and consequently reach the alveoli evading the mucociliary clearance mechanisms. The sources of the bacilli are subjects with *sputum positive* disease, who also have the highest case-fatality rate. The probability that a susceptible individual will become infected depends on the concentration of infectious droplet nuclei in the air. Factors affecting this include the presence of cavitation or extensive pulmonary infiltrates, presence of a forceful cough (especially if associated with an unwillingness to cover one's mouth while coughing), high volume and low viscosity of sputum, prolonged duration of respiratory symptoms, indequate chemotherapy and overcrowding. Household contacts of a sputum-positive patient are at the greatest risk of acquiring infection. Fomites play no role in the transmission of tuberculosis. Rarely, the disease can be due to *M. bovis* acquired by drinking unpasteurised milk from infected cows (mainly in the tropics).

Magnitude of problem in the developing countries: It has been estimated that the annual risk of infection in developing countries is 1–2%. The incidence of smear-positive cases is about 77 per 100,000. Based on an estimate of about 1.2 smear-negative cases and extrapulmonary disease for every smear-positive case, the incidence is 171 cases of disease per 100,000. About 80 per cent of those affected are in the 15–55 years age group. Tuberculosis is the leading cause of death from a single pathogen worldwide. It accounts for 18 per cent of all deaths and 25 per cent of preventable deaths in the age group 15–55 years.

One epidemiologic method of estimating tuberculosis infection is tuberculin sensitivity. Tuberculin sensitivity can be tested by an intradermal injection of 0.1 ml of PPD (purified protein derivative; 1 TU) and measuring the diameter of the area of skin induration at 48–72 hours (Mantoux test). Tuberculin sensitivity is a measure of infection with tuberculosis, not disease. An area of induration greater than 10 mm suggests a positive test while one less than 5 mm is a negative test. Generally, individuals with a reaction of >15 mm or of <5 mm are at greatest risk of developing disease. There are some limitations to the use of the Mantoux test as an index of tubercular infection. Prior BCG vaccination, prior tuberculin testing, exposure to atypical mycobacteria are associated with

positive tuberculin tests while the presence of severe tubercular disease, HIV infection or the use of an improper test technique can lead to a negative Mantoux test.

Pathogenesis

Primary infection: Tubercle bacilli usually reach the lower two-thirds of the lung (where ventilation is maximum) in high concentration: this area is the *primary focus.* In the host who has not previously been exposed, the organisms are phagocytosed by alveolar macrophages. The bacilli multiply within the macrophages and are carried to the regional lymph nodes and also throughout the body. After an incubation period of 3 to 6 weeks, T lymphocytes sensitised to the tubercle bacilli activate the macrophages to kill the intracellular bacilli. This results in an acute exudative response—the *tuberculous granuloma* —in all the tissues where the bacilli were lodged. The granuloma consists of a focal collection of mononuclear epitheloid cells, multinucleate giant cells (Langhans' giant cells) and caseation necrosis. The caseous necrosis is due to destruction of the bacteria with a release of mycolic acids. The primary focus, the involved regional lymph nodes and lymphatics between them constitute the *primary (Ghon) complex.* The primary complex heals with fibrosis and calcification and a state of balance is established between the multiplication of intracellular bacilli and macrophage killing of the bacilli.

Dormant infection: During the early dissemination of bacilli, several organs are seeded with tubercle bacilli latent within the macrophages. The organs with the highest oxygen tension (>90 mmHg) are ideal for bacillary growth; the apex of the lungs are the preferred sites of secondary dissemination and these lesions are called *Simon's foci.* The growing metaphyseal ends of long bones, the vertebral column and the renal cortex are other preferred sites. The primary intracerebral lesion is called *Rich's focus.* In people who have developed hypersensitivity to the tubercle bacilli, the subsequent inhalation of bacilli results in rapid mobilisation of the immune response and the elimination of organisms before replication or dissemination. However, 5–10% of subjects with tuberculosis infection develop disease within 1 to 2 years of infection. A further 5–10% develop recrudescence of dormant lesions later in life.

Clinical disease: The clinical disease results from the recrudescence of dormant infection under conditions when the host immune response against the tubercle bacilli wanes (due to age or immunosuppressive states such as HIV infection). The symptoms and signs of tuberculosis are not due to the invading bacilli but due to the host immune response. Activation of T lymphocytes results in the release of macrophage-activating factors and the monokine — 'tumour necrosis factor/cachectin'. This monokine is responsible for chronic low-grade pyrexia and also mediates the caseation necrosis in tuberculous granulomas. The caseating granulomas lead to tissue destruction and organ dysfunction.

Pulmonary tuberculosis

Pulmonary tuberculosis is the commonest presentation of tubercular disease, accounting for upto 90 per cent of all clinical tuberculosis. Two forms of the disease are recognised and are discussed below.

Primary pulmonary tuberculosis Primary pulmonary tuberculosis can present as one of four broad clinical syndromes. It is usually symptomless except for the occasional presence of low grade fever of 1 to 2 weeks duration. Erythema nodosum and phlyctenular conjunctivitis may be seen and are manifestations of hypersensitivity to mycobacteria. The chest X-ray is usually normal. If the primary complex does appear, it may progress for 1 to 2 months, may not diminish for another 3 to 4 months and may remain visible, though smaller, for 6 to 12 months. Left lung lesions may be associated with uni- or bilateral hilar adenopathy

whereas right lung lesions are associated with only ipsilateral adenopathy due to the pattern of mediastinal lymphatic drainage. Calcification of both the parenchymal and the hilar foci may occur and usually indicates that the lesions are at least 6 months old. Calcification indicates a good prognosis. Occasionally, the paratracheal and peribronchial lymph nodes may produce collapse of a segment of a lung or a lobe by compression of the bronchus.

The second syndrome is that of tuberculous pleuritis with effusion. The disease is more common in older children, is usually unilateral (on the same side of the primary lesion) and affects males twice as often as females. It is usually a result of the extension of a subpleural focus. These patients present with high fever and pleuritic chest pain; dyspnea and tachypnea may be present if the effusion is large. The pleural fluid is an exudate.

A third form of the disease is characterised by progressive pulmonary lesions with cavitation. Such a course is more common in adults. Occasionally in children, primary pulmonary tuberculosis is associated with segmental collapse due to extrinsic bronchial compression by enlarged peribronchial lymph nodes.

Reactivation tuberculosis This form of tuberculosis is seen in adults. Foci with dormant tubercle bacilli in the posterior portions of the upper lobe become reactivated. This results in systemic and local symptoms. Systemic features include low-grade fever, night sweats, anorexia, malaise and fatigue. Local symptoms include hemoptysis, a productive cough and pleuritic chest pain. Reactivation tuberculosis differs from the primary disease in that chronicity, cavitation and progression are more common but lymph node involvement is minimal. The presence of rales in the lung apices is a typical sign. Chest X-ray films further corroborate the diagnosis when apical infiltrates or cavities are noted. A definitive diagnosis of tuberculosis requires microbiologic proof: demonstration of acid-fast bacilli on Ziehl-Nielsen staining of sputum smears or on sputum culture (on the Lowenstein-Jensen medium).

Tubercular pleurisy with effusion occurs in young adults. The disease may have an acute or an insidious onset. Fever, pleuritic chest pain on the affected side and breathlessness (in the case of large effusions) are important symptoms. A pleural friction rub and evidence of an effusion on physical examination are important signs. Thoracentesis yields a straw-coloured exudate with a predominance of lymphocytes. Elevated pleural fluid adenosine deaminase (ADA) levels also suggest a tubercular etiology of the effusion. Tubercle bacilli are usually scarce in the fluid. An examination of the pleural tissue obtained by a closed needle biopsy may provide confirmatory evidence (caseating granulomas).

Table 8.16 Clinical spectrum of extrapulmonary tuberculosis

Category	*I*	*II*	*III*
Example	miliary tuberculosis, tubercular meningitis, pericarditis	tubercular peritonitis, pleuritis	tuberculosis of individual organ systems: lymphadenitis, osteomyelitis, genitourinary, hepatic
Onset	acute/subacute	chronic	insidious
Progression	rapid, life-threatening	slow	slow
Systemic symptoms	febrile	febrile	may often be afebrile
Tuberculin skin test	negative in 20%	usually positive	almost always positive

Treatment of pulmonary and pleural tuberculosis is discussed subsequently.

Extrapulmonary tuberculosis

Extrapulmonary tuberculosis may be thought of as consisting of three categories of illness (Table 8.16). Some forms of extrapulmonary tuberculosis are discussed below:

1. **Miliary Tuberculosis**

The term 'miliary' tuberculosis derives its name from the widespread pathological presence of macroscopically visible lesions that resemble millet seeds. Hematogenous dissemination is universal in the course of the initial infection with tubercle bacilli. Recrudescence of these latent lesions or a second episode of dissemination (such as due to the rupture of a caseous lesion into a vein) underlies the pathogenesis of milary tuberculosis.

The disease has a peak incidence in infants, young children and the elderly; an increase in incidence has recently been recognised in young adults who are HIV-positive. The disease has a subacute onset and symptoms progress over a period of one to four months. Fever is an important clinical feature in two-thirds to three-quarters of patients. Anorexia, nausea, vomiting and weight loss are common. Pulmonary symptoms are non-specific and include cough and dyspnea (60%). Headache is important as it may indicate meningeal involvement. Occasionally, fulminant pulmonary disease may present with respiratory failure. Uncommon presentations include manifestations of disseminated intravascular coagulation, anemia, leukemoid reaction or myelofibrosis. Some patients present with fever of undetermined origin with no localising features and a normal chest X-ray (cryptic miliary tuberculosis).

A physical examination may reveal pulmonary findings (50%), hepatomegaly (30%), lymphadenopathy and splenomegaly (15%). Choroidal tubercles are uncommon but more specific. Laboratory findings are also non-specific and include a variety of hematologic findings (ranging from pancytopenia to a leukemoid reaction). Elevation of levels of hepatic alkaline phosphatase may be seen (30%) as miliary tubercles are interstitial. A liver biopsy may be diagnostic in about 60 per cent of patients whereas a bone marrow biopsy reveals caseating granulomas in a third of patients. The tuberculin skin test is often negative. Bronchoscopic brushings may be positive in about 70 per cent of patients. A clinical trial of antitubercular therapy is sometimes necessary to exclude the diagnosis when all ancillary tests are negative.

Without treatment miliary tuberculosis is uniformly fatal. With treatment the mortality has been reduced to 5–35 per cent. Extremes of age, the presence of meningeal involvement and HIV-positive status are adverse prognostic factors.

2. **CNS Tuberculosis**

The most commonly recognised site of clinically severe extrapulmonary tuberculosis is the central nervous system. The clinical syndromes include 1) tuberculous meningitis, 2) tuberculoma of the brain, 3) miliary parenchymal disease, 4) serous meningitis and 5) vascular and localised syndromes due to destructive lesions associated with the above.

Tuberculous meningitis: This is the commonest of the CNS syndromes listed above. The disease affects about 2 to 5 per cent of children with untreated tuberculous infection.

Pathogenesis The primary intracerebral lesion (Rich's focus) ruptures into the subarachnoid space and results in the seeding of the meningeal surfaces. The meningitis provokes a characteristic inflammatory reaction around the base of the brain. The cranial nerves at the base of the brain (3rd, 6th, 8th, 9th, 10th, 11th) are injured, which explains the optic and auditory complications. The thick basilar exudates also produce obstruction to the flow of the cerebrospinal fluid resulting in *hydrocephalus*. Other secondary effects of the basilar exudates include the production of arteritis (resulting in

infarcts), infiltration of the veins (resulting in hemorrhage) and the invasion of small cortical vessels (resulting in abscesses).

Clinical features The onset of disease can be rapid in 50% of patients (< 14 days) but is chronic in the rest (2 to 6 months). The initial stages of the illness are characterised by fever, malaise, irritability and anorexia (Stage I). With disease progression, findings attributable to neurologic injury become more evident (Stage II). Headache, neck pain and stiffness, cranial nerve palsies, vomiting and drowsiness are prominent features of this stage. Stage III is identified by the onset of an alteration in the level of consciousness; stupor or unconsciousness sets in at this stage. Seizures, advanced hydrocephalus and brainstem or parenchymal infarction are other features of this stage of the disease.

Diagnosis and treatment A lumbar puncture with cytological examination of the CSF remains the investigation of choice. The CSF findings vary with the stage of the disease. Very early in the disease, there may be a polymorphonuclear leukocytosis with mild elevation of CSF protein content and a glucose level approximately 50 per cent that of serum. With disease progression, the findings are more characteristic. Typically, the cell count varies from 100–1000 cells /mm^3, with more than 70% being lymphocytes or mononuclear cells. The protein content is also elevated, ranging from 50–200 mg/mm^3. A marked elevation of CSF protein may suggest a block in the CSF absorption pathway. CSF glucose levels fall to 10–25% of serum glucose levels. A Ziehl-Nielsen stain of the CSF demonstrates acid-fast bacilli in only 25% but culture of CSF can identify the tubercle bacilli in upto 75% of patients. In select centres it is possible to diagnose the disease with the use of the polymerase chain reaction to detect mycobacterial DNA in the CSF or by the detection of tuberculostearic acid in the CSF. Basilar meningitis can be identified by a CT scan of the brain in upto a third of patients and suggests a diagnosis of tubercular meningitis. Choroidal tubercles can be seen in upto 10 per cent of patients on careful examination of the fundus and are helpful clinical signs if the CSF smears and cultures are non-diagnostic. *Early diagnosis must be made as quickly as possible as any delay can cause permanent neurologic deficit.*

Early differentiation from other causes of chronic meningitis or lymphocytic meningitis (particularly cryptococcosis) is important and an India ink preparation of the CSF may be obtained if the smear for acid-fast bacilli is negative. The other diagnostic possibilities include partially treated bacterial meningitis, fungal meningitis and carcinomatous meningitis. If bacterial and fungal stains, serologies and cytologies are negative, empirical antitubercular therapy must be promptly instituted. Some authorities believe in starting both antitubercular and antibacterial therapy. If the diagnosis is a partially-treated bacterial meningitis, clinical response is rapid and the antitubercular drugs can be stopped. If there is no clinical response after a course of antibacterial drugs, they are discontinued and the antitubercular drugs continued. The advantage of this approach is the early institution of antitubercular drugs without delay.

Isoniazid and rifampicin must be a part of any regimen for tubercular meningitis. Corticosteroids are useful if there is evidence of cerebral edema or subarachnoid block. Ventricular shunting is a surgical measure which is useful in patients with hydrocephalus who do not respond to antitubercular therapy or diuretics.

Prognosis Morbidity and mortality vary with the stage of disease at which treatment is commenced. Thus mortality for Stage I, II and III disease ranges from 5 to 20%. The incidence of neurologic sequelae similarly varies from 20% (Stage I) to 70% (Stages II and III). On the average, about a third of patients die, another

third have neurologic sequelae and the other third recover completely.

Tuberculoma of the brain: The term tuberculoma refers to a large tubercular lesion of the brain that produces a mass effect and has an inflammatory component. It is the equivalent of an encapsulated pyogenic brain abscess.

Tuberculomas are more common in young children although no age group is exempt. They are most common in the supratentorial areas such as the frontal, parietal and occipital cortex. Children are more likely to have infratentorial lesions. There are three clinical presentations:
1. signs and symptoms of a mass lesion (include headaches, nausea and vomiting) suggesting increased intracranial pressure. Infratentorial lesions present earlier due to an increased likelihood of such symptoms;
2. development of focal neurologic deficits dependent on the location of the lesion;
3. routinely detected lesion during CNS imaging for a person suspected of having tuberculosis elsewhere.

Tuberculomas are often diagnosed as tumours before surgery. If an intracranial tuberculoma is strongly suspected, a trial of chemotherapy is preferable as these lesions respond well to medical management. The clinical outcome is excellent. Sometimes new tuberculomas may develop paradoxically during treatment; this may be related to a heightened immunological reaction to the tuberculin antigen manifesting at subclinical foci.

Miliary tuberculosis of the CNS: This condition has been increasingly recognised with the advent of CNS imaging with CT or MRI scans. Low-grade bacillemia of primary tuberculosis can lead to small granulomata that are subclinical and associated with a normal CSF examination. The lesions are incidentally revealed during the course of investigations for tubercular meningitis or tuberculosis elsewhere. They respond to the therapy of the primary tubercular disease.

Serous meningitis: This is a rare syndrome characterised by mild CSF pleocytosis and protein elevation provoked by a tubercular granuloma that lies adjacent to the subarachnoid space but has not ruptured. It presumably represents a mild form of meningitis adequately checked by the host defense responses. The condition does not progress to frank tubercular meningitis and is difficult to recognise clinically.
Vascular complications: Children with intracranial tuberculosis can develop an inflammatory arteritis of medium and large vessels that can result in infarction of tissue supplied by the affected vessels. The clinical presentation varies from a stroke syndrome to focal neurologic deficits. Vascular involvement signifies a poor prognosis and major residual deficits are not uncommon. MRI scans demonstrate vascular lesions in the brainstem and temporal lobe.

3. **Osteoarticular Tuberculosis**

Tuberculosis of the bones can take the form of either tubercular osteomyelitis or tubercular arthritis. Roughly 1 per cent of children with tuberculosis develop a bony focus. These foci can be reactivated to result in a slowly progressive osteomyelitis with involvement of joints and soft tissues. The overlying skin can be involved by the formation of chronic discharging sinuses. Unlike a bacterial osteomyelitis, there is no periosteal reaction, roentgenographic evidence of sclerosis of bony margins does not occur and there is no point of tenderness at the infected site. Involvement of the synovial surfaces can result in arthritis. Progressive destruction of the joints results in a *fibrous ankylosis*. Spread to adjacent soft tissues can result in so-called *cold abscesses.*

Though bone or joint tuberculosis can manifest early (within 2 years of infection) or late, symptoms often begin in childhood and adolescence. Large joints like the hip, knee, wrist, elbow, and shoulder, and bones like the spine are commonly involved. In developing countries any monoarticular arthritis should raise suspicion of tuberculosis.

Tubercular spondylitis (Pott's spine): The spine is the commonest site of skeletal tuberculosis (50% of all cases of skeletal tuberculosis). The dorsal and lumbar vertebrae are more often involved than the cervical vertebrae. Typically multiple vertebral bodies are involved. The infection usually spreads to the intervertebral disc spaces and the vertebral bodies get eroded. Collapse of the vertebral bodies results in wedge-shaped deformities of the vertebrae. Collapse of multiple vertebrae can result in angulation of the back, the *gibbus* deformity which is typical of tubercular infection of the spine. The tubercular pus may track down between fascial spaces resulting in paraspinal abscesses. A *psoas abscess* is a typical example of pus tracking down the planes of the iliopsoas muscle. As the disease progresses, involvement of the adjacent neurologic structures is common. The tubercular vertebral abscess can compress the spinal cord from outside (*extradural compression*); paraplegia is a common complication occurring in upto 15 per cent of patients. The vessels supplying the spinal cord may be affected leading to spinal cord infarction. Nerve compression can result from inflammation of the pia arachnoid investing the spinal cord — tuberculous arachnoiditis. Late neurologic complications may arise due to spinal cord compression by scar tissue or bony spicules.

Management includes obtaining tissue for diagnosis, antitubercular drugs, analgesics for the relief of pain and debridement of dead bone. Immobilisation of the spine is currently believed to play a minor role.

Tubercular dactylitis: Tuberculosis of the flat bones of the hands and feet is called tubercular *dactylitis*. These lesions present as severe pain in the involved finger or toe and the typical X-ray shows a cystic lesion with prominent bony spicules, also called spina ventosa, which are painless and sometimes heal spontaneously.

Tubercular arthritis: The hip joint is the commonest site of tubercular synovial infection (20% of all skeletal tuberculosis). It may arise from infection of the femoral head and the common symptoms are pain in the hip and progressive gait disturbances.

The synovial fluid in tubercular arthritis is characterised by a high protein content, a low glucose, and a white cell count of 10,000–20,000/mm^3 (predominantly neutrophils). Though smears of the synovial fluid demonstrate acid-fast bacilli in only 20% of patients, synovial fluid culture and biopsy are positive in 80–90% of patients. Response to chemotherapy is excellent but occasionally surgery may be required for the fusion of destroyed joints.

4. **Tubercular Lymphadenitis**

Tubercular lymphadenitis is the commonest form of extrapulmonary tuberculosis. The cervical lymph nodes are the most commonly affected. The pathogenetic mechanism is not clear but seeding from a pulmonary source or an inapparent focus in the upper respiratory mucosa may play an important role. The anterior cervical lymph nodes are more often involved. The affected lymph nodes become enlarged and firm, and inflammation of the capsule leads to periadenitis. Consequently, the lymph nodes are matted together and soft areas of liquefaction necrosis lead to fluctuation. The fluctuant lymph nodes may burst open and discharge the caseous material into the overlying subcutaneous tissues. Finally, chronic sinuses discharge the material outside. Pain is uncommon but associated features of fever, weight loss and anorexia are common. Often there is no evidence of pulmonary or extra-pulmonary foci of tuberculosis.

The diagnosis is established by demonstrating acid-fast bacilli in the material aspirated from the lymph nodes. Lymph node biopsy may be considered if aspiration cytologies are repeatedly negative. The differentiation from cervical adenitis due to non-tubercular mycobacteria may be especially difficult but making the distinction is important as the latter disease does not respond to chemotherapy,

making surgical excision the treatment of choice. A history of contact with a patient with tuberculosis (50%), preferential involvement of the posterior cervical or axillary nodes, bilaterality of involvement, a positive Mantoux test, and an abnormal chest X-ray (15–20%) favour a diagnosis of infection with *M. tuberculosis.* Incision and drainage are not preferred in the treatment of any mycobacterial infection of lymph nodes as there is a high likelihood of chronic sinus formation.

The involvement of the perihilar lymph nodes is universal in all the forms of pulmonary tuberculosis but does not usually pose any problems. In infants and young children, the right middle lobe bronchus may get compressed resulting in a *middle lobe syndrome* characterised by chronic infection and atelectasis of the affected lung. The disease may later be complicated by bronchiectasis.

The involvement of the mesenteric lymph nodes may be acute, taking the form of severe acute pain in the abdomen (so-called *tabes mesenterica*), or chronic, presenting as a palpable abdominal mass consisting of rolled-up omentum and abdominal lymph nodes.

5. Abdominal Tuberculosis

Several syndromes are encompassed by the term abdominal tuberculosis: intestinal tuberculosis, peritoneal tuberculosis, renal tuberculosis, hepatic tuberculosis and genitourinary tuberculosis. Renal and intestinal tuberculosis are discussed extensively in the sections on renal and gastrointestinal disease.

Tubercular peritonitis: Tubercular involvement of the peritoneum arises from hematogenous seeding during the primary bacillemia, or from the extension of tubercular salpingitis, enteritis or mesenteric lymphadenitis. There is an initial *exudative* phase characterised by free fluid in the peritoneal cavity followed by a *plastic* phase with extensive fibrosis of the involved structures. In the latter phase, there is clinical evidence of a *doughy* feel of the abdomen due to palpation of matted loops of the omentum, bowel and lymph nodes. Fever, abdominal pain and increasing abdominal girth are the commonest symptoms.

Paracentesis yields a straw coloured fluid; a serosanguinous fluid is uncommon and suggests *peritoneal carcinomatosis.* Examination of the ascitic fluid reveals high protein levels (>30 g/L), a high cell count (100–3000/mm^3, average of 500/mm^3 and with 75% lymphocytes) and elevated LDH levels. Estimation of the ascitic fluid/blood glucose is useful as a ratio below 0.96 strongly suggests tubercular involvement. Acid-fast bacilli are generally not demonstrable in smears or cultures unless extremely large volumes of fluid are subjected to examination. A peritoneal biopsy, guided by a *minilaparoscopy*, has a higher yield.

Untreated, the mortality may be as high 50 per cent with a high incidence of bowel obstruction in survivors. With chemotherapy, however, the prognosis is excellent.

Genitourinary tuberculosis: In men genital tuberculosis usually involves the seminal vesicles and the prostate gland. Fifty per cent of patients have coexisting renal tuberculosis. The clinical presentation includes painful ejaculation, pain and swelling of the epididymis and dysuria. Sometimes patients present with slowly enlarging mass lesions of the epididymis, prostate or the seminal vesicles; tuberculosis is diagnosed incidentally by aspiration of the mass.

In women genital tuberculosis is usually the consequence of hematogenous dissemination. The fallopian tubes (100%), the uterus (90%), the ovaries (20%) or the cervix (<1%) may be involved. The presenting symptoms include infertility, amenorrhea, pelvic pain or abnormal menstrual bleeding. A physical examination may reveal an adnexal mass. Diagnosis is based on pelvic sonography, endometrial curettage or a minilaparotomy (for the diagnosis of *tubo-ovarian abscesses*).

Hepatic tuberculosis: Tuberculosis of the liver may present as part of a miliary process or rarely, as a tuberculoma. Approximately 25 per cent of patients have concomitant peritoneal

involvement. The diagnosis is suspected on the basis of elevated levels of alkaline phosphatase and is confirmed by ultrasound- (or CT-) guided liver biopsy. Sometimes a laparoscopic-guided biopsy of the granulomas on the liver surface may be performed as an alternative to 'bind' liver biopsy.

6. **Tubercular Pericarditis**

Tubercular infection of the pericardium may result from hematogenous dissemination or may develop by contiguous spread from the infected lymph nodes or pleuropulmonary tissue. The pathological changes range from an effusion to frank pericardial constriction.

The inflammatory process begins with insidious onset of fever, substernal pain and shortness of breath. Pain is present in only 50 per cent and a pericardial friction rub is heard in 33 per cent of patients. Pericardial tamponade is common and identified by the clinical presence of a paradoxical pulse, jugular venous distension and a palpable tender liver. The presence of an effusion can be documented with an echocardiographic examination and pericardiocentesis is performed to obtain fluid for analysis. The pericardial fluid may be turbid or hemorrhagic, with an elevated white cell count (5000– 10,000/mm^3 with a predominance of lymphocytes), elevated protein content and low glucose levels. Smears and cultures of pericardial fluid are positive in less than half of the patients; pericardial biopsy has a higher diagnostic yield. If untreated, the mortality is high (80%) and pericardial constriction occurs in many survivors.

Antitubercular therapy must be instituted early. Surgery (pericardiectomy) is required for tamponade that does not improve with pericardiocentesis or progresses. Corticosteroids have been shown in some studies to reduce the incidence of pericardial constriction and overall mortality.

7. **Tuberculosis of the Skin**

Lupus vulgaris refers to skin lesions due to dermal reactivation of mycobacteria; the lesions are discoloured and raised. Tubercle bacilli are sparsely present in these lesions. *Erythema nodosum* lesions are tender, painful, raised discoloured lesions occurring on the shins and thighs; tubercle bacilli are not seen in these lesions that represent an immune reaction towards the tubercle antigen. These lesions are not specific to tuberculosis as they are also seen in streptococcal disease, yersiniosis and drug reactions.

8. **Tuberculosis with Endocrine Dysfunction**

Adrenal tuberculosis: The tubercle bacilli occasionally lodge in the adrenal glands during hematogenous dissemination and the granulomatous inflammation within the adrenal cortex can lead to adrenocortical insufficiency (Addison's disease). The clinical features are similar to adrenocortical dysfunction due to any other etiology and include progressive weakness, pigmentation of the skin and oral mucosa, malaise, lethargy, anorexia and postural hypotension. Serum sodium is reduced and serum potassium levels are elevated. The diagnosis is suspected if there is radiologic evidence of adrenal calcification in the presence of the clinical features detailed above. Low plasma cortisol levels and increased plasma ACTH levels help to confirm the diagnosis. Treatment consists of antitubercular chemotherapy, corticosteroid replacement and correction of electrolyte imbalances.

Syndrome of inappropriate secretion of antidiuretic hormone: This disorder usually occurs in elderly subjects with overwhelming infection with the tubercle bacilli. The patient is somnolent, the serum sodium is low (<120 mmol/L) and the serum osmolality is low (<270 mosmol/L). Urine is hypertonic relative to the plasma. Antitubercular therapy is combined with water restriction.

Prevention of tuberculosis The three major strategies for tuberculosis prevention are

1. BCG vaccination,
2. preventive isoniazid therapy, and most importantly

3. case finding and treatment.

BCG[1] is a live attenuated vaccine. There are uncertainties regarding the efficacy of BCG. Several large trials have demonstrated varying efficacy ranging from 0 to 80 per cent. The largest trial was conducted in the Chingleput district of Tamil Nadu and showed no protection against pulmonary tuberculosis. The present consensus is that BCG vaccination does not prevent either primary pulmonary tuberculosis or reactivation tuberculosis in adults. However, it does provide protection against hematogenous dissemination from the primary complex, thereby reducing the incidence of severe forms of tuberculosis (such as meningeal tuberculosis) by 75 to 90 per cent. Further, it also reduces mortality due to tuberculosis in children, by about 6 per cent. The BCG vaccination has little impact on the epidemiology of tuberculosis as it does not reduce the transmission of tuberculosis in the community. Nonetheless the WHO supports the use of BCG vaccination as part of the expanded programme of immunisation.

Preventive INH therapy (defined as isoniazid treatment for 6 to 12 months) can prevent the development of disease in people infected with the tubercle bacillus by upto 90 per cent. However, infection with the tubercle bacillus is so common in developing countries that resources are better directed toward case finding and treatment. An exception is the contact of a patient who undergoes tuberculin conversion and is less than 5 years of age.

Case finding may be passive or active. Passive case finding is the detection of tuberculosis in patients attending health clinics. The effectiveness of this method is limited by a lack of awareness of tuberculosis, poor case management and inaccessibility of health centres. Active case finding among whole populations is generally not used in developing countries because of the high cost and low yield. Mass miniature radiography is expensive and unreliable. Mantoux testing is not useful as there is a very high infection rate in developing countries and the test may be negative with malnutrition, HIV infection and severe disease. Short course chemotherapy offers the best cure rates for the disease and is the most effective method of preventing tuberculosis in developing countries.

Antitubercular chemotherapy

Chemotherapy for tuberculosis differs from that of other bacterial infections in two important ways: 1) multiple drugs are required, and 2) the drugs must be administered for a prolonged duration. Multiple drugs are required in order to prevent the emergence of drug-resistant organisms (Fig 8.8). Prolonged chemotherapy is necessary because the tubercle bacilli multiply slowly and can lie dormant for a long period.

Older regimens of antitubercular therapy employed multiple drugs for periods of 18 to 24 months. In recent years, shorter regimens utilising combinations of newer agents for six to nine months have been found to be equally effective, more economical and are associated with a greater compliance.

These short course chemotherapy regimens consist of two phases: an initial intensive phase consisting of 4 drugs (usually for 2–3 months) followed by a consolidation phase consisting of INH and one other drug (for another 4–9 months based on drugs used). Isoniazid possesses the best combination of high effectiveness, low frequency of side effects and cost, and should be used whenever possible. Pyrazinamide (given in the initial phase) improves the efficacy of regimens that are shorter than 9 months; ethambutol or streptomycin are less effective in comparison to pyrazinamide. If a six month regimen is used, both INH and rifampicin must be a part of the drug combinations throughout the period. The regimen may consist of daily administration of drugs or the drugs may be administered intermittently (twice a week with appropriate adjustment of doses). When using a daily regimen, single daily doses of drugs are

[1] Named after two French physicians Calmette and Guerin who developed the attenuated strain initially

preferred over divided doses. An important component of the treatment is the follow-up of patients to ensure compliance and to monitor drug efficacy and toxicity. Indeed, the major determinant of the treatment outcome is patient compliance. Therefore, consideration should be given, whenever possible, to directly observed therapy (*DOT*). DOT means observation of the patient by a health care provider or another person, as the patient takes her medicine. DOT is an attractive option of ensuring compliance under field conditions.

In the developed countries, a six-month regimen consisting of isoniazid, rifampicin, and pyrazinamide given for 2 months, followed by isoniazid and rifampicin for 4 months has been found to be very effective. In developing countries, ethambutol (or streptomycin, in children too young to be monitored for visual acuity) may be added to the initial regimen; this four-drug, six-month regimen is effective even when the organism is resistant to INH. Alternatively, a nine-month regimen of INH and rifampicin is acceptable for persons who cannot or should not take pyrazinamide (see below); ethambutol or streptomycin may be added to this regimen for the initial 2 months. Another common and highly effective regimen is the use of streptomycin, isoniazid, rifampicin and pyrazinamide (SHRZ) together for three months followed by rifampicin and isoniazid (RH) alone for another six months. In developed countries, it has been suggested that individuals with active pulmonary tuberculosis who are negative on sputum smear and culture, may be treated with a four-month regimen of INH and rifampicin. The applicability of this regimen in developing countries is not clear. The above treatment regimens are recommended for both human immunodeficiency virus (HIV) infected and uninfected persons. In the presence of HIV infection, it is all the more critical to assess clinical and bacteriologic response. If there is a slow or suboptimal response, therapy may be prolonged. In developing countries, patients with mild disease may be treated with a regimen consisting of INH and ethambutol for 12–18 months. One of the least expensive regimens consists of INH and thiacetazone daily for 12–18 months; this regimen is not as effective as a regimen with rifampicin but the addition of streptomycin for the initial 8 weeks improves efficacy (but doubles cost).

Symptomatic improvement is evident within the first 2–3 weeks in most patients. Patients become afebrile, demonstrate improvements in appetite and body weight. The patient appears less toxic and the elevated ESR begins to decrease. Improvements in sputum bacteriology and radiographic appearance follow, often in tandem with this clinical response.

Sputum smear examinations at monthly intervals is desirable for all patients who are smear-positive initially. This is one of the best ways of assessing therapy. Generally, after 2 months of treatment with a regimen containing INH and rifampicin, the sputum becomes negative (for M. tuberculosis) in over 85 per cent of patients. Patients whose sputum becomes negative after 2 months of antitubercular treatment should have at least one further smear performed on completion of therapy. Patients whose sputum has not become negative after 2 months of treatment must be reevaluated; non-compliance and drug-resistance are possibilities. In the case of treatment failure, drugs should be changed in combination, rather than singly. Non-responders may harbour drug-resistant organisms; therefore, the introduction of a single new drug may lead to the development of resistance to the new agent by permitting the selection of organisms resistant to the new drug. Such treatment failure is often best managed in consultation with an expert in the field.

Chest radiographs are also an important means of assessing therapeutic responses. Clearing of the parenchymal infiltrates begins within the first month and becomes clearly evident between the second and fourth month of therapy. The failure of the chest radiograph to improve after 3 months of therapy suggests that

either the organism is resistant, or the patient non-compliant, or the abnormality may be the result of another process (or previous tuberculosis).

Most short-course chemotherapeutic regimens achieve cure rates in excess of 90–95 per cent. Relapses after cure occur in fewer than 2–3 per cent of patients, usually occurring within the initial year. Failure to respond is often due to patient default; default rates as high as 40–60 per cent are seen in developing countries, emphasising the importance of DOT.

Special situations

a. *Tuberculosis in children and adolescents*: These groups can generally be managed in the same way as outlined for adults. Sputum smears are less useful in children and clinical and radiographic examinations are more important for monitoring response to treatment. Since hilar adenopathy may take upto 2–3 years for resolution, a normal chest radiograph is not a necessary criterion for assessing response.

b. *Extrapulmonary tuberculosis*: Patients with extrapulmonary tuberculosis are much less infectious. Generally, extrapulmonary tuberculosis can be managed according to the same principles outlined for pulmonary disease, except for children who have miliary tuberculosis, bone/joint tuberculosis, or tuberculous meningitis. These patients should receive a minimum of 12 months treatment. Adjunctive therapy such as surgery and corticosteroids may be required for extrapulmonary tuberculosis. Corticosteroids have been specifically shown to reduce the incidence of cardiac constriction from tuberculous pericarditis and also decrease the neurologic sequelae of tuberculous meningitis (especially when administered early in the disease).

c. *Pregnancy and lactation*: Tuberculosis poses a greater hazard to pregnant women than treatment does to the fetus. Tuberculosis during pregnancy is not an indication for abortion. INH, rifampicin and ethambutol all cross the placenta but are not teratogenic. Streptomycin is avoided as it can damage the inner ear of the fetus. Opinions vary regarding the appropriateness of pyrazinamide use in pregnancy because of inadequate data on its teratogenic potential. Pyridoxine supplementation is important in the pregnant woman on INH. Breastfeeding should be encouraged as the small concentrations of antitubercular drugs in breast milk do not pose any risk to the newborn.

d. *Renal failure*: Patients with renal failure are at tenfold increased risk for tuberculosis compared to the general population. Doses of most antitubercular drugs other than rifampicin need to be changed in these patients. The dose of INH must be reduced to 5 mg/kg and the drug should be given 2–3 times a week (not daily), (preferably after each dialysis in patients on dialytic support). Ethambutol may be used but the usual daily dose is given at longer intervals (preferably after dialysis) and the patient more carefully monitored for ocular toxicity. The major antitubercular drugs and their doses are listed in Table 8.17.

First-line antituberculous agents

Isoniazid: Isoniazid (INH) is bactericidal but is active only against dividing mycobacteria. Its mechanism of action probably involve inhibition of the synthesis of mycolic acid as well as of mycobacterial DNA. INH has excellent tissue penetration. The drug is metabolised by hepatic acetylation followed by renal excretion of the metabolites. The rate of hepatic acetylation is a genetically determined trait.[1] Peripheral neuropathy is somewhat more common in slow acetylators whereas isoniazid hepatotoxicity may be more common in rapid acetylators. It is not necessary to modify the INH dosage except in advanced renal failure. Isoniazid is inexpensive and the usual oral dose is 5 mg/kg body weight, which averages 300 mg/day for the adult. A parenteral preparation (for intra-

[1] The half-life of isoniazid averages 80 minutes in rapid acetylators and 180 minutes in slow acetylators.

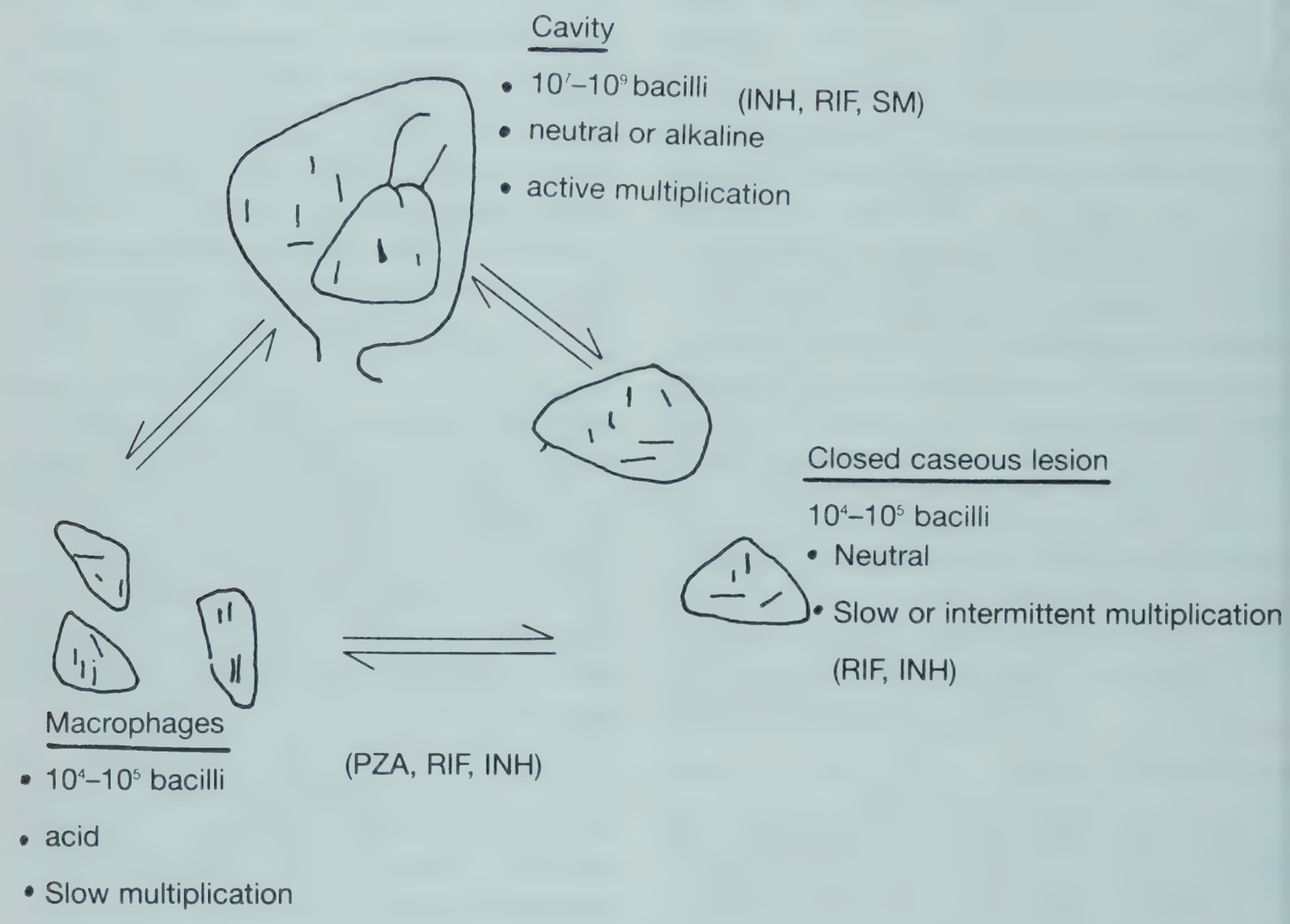
muscular use) is also described, although commercial availability is limited. The major toxicities associated with INH use include hepatitis, peripheral neuritis and hypersensitivity reactions (fever, rash, and rheumatic syndromes with or without positive antinuclear antibodies). Pyridoxine supplementation (50 mg/day) is recommended for patients receiving INH in order to prevent peripheral neuropathy. Neurologic toxicity of INH also includes less common manifestations such as encephalopathies, seizures, optic neuritis, and personality changes. Although clinically significant, hepatitis appears in fewer than two per cent of patients receiving INH, a transient rise in aspartate aminotransferase (AST) is seen in 10 to 20 per cent of cases. Mild transient AST elevations do not necessitate drug withdrawal in asymptomatic patients; a close follow-up is, however, judicious. Isoniazid must be stopped if mild AST elevations persist, or if signs or symptoms of hepatitis appear. Isoniazid interacts with a variety of drugs; it increases serum levels of phenytoin, carbamazepine, primidone and barbiturates, and decreases serum levels of ketoconazole.

Rifampicin: Rifampicin rivals INH in its antitubercular efficacy. Unlike isoniazid and ethambutol, rifampicin is a broad-spectrum antimicrobial agent which acts against some atypical mycobacteria, and many bacteria (including staphylococci, meningococci, and various gram-negative bacilli). A therapeutic trial of antitubercular therapy, therefore, should not include rifampicin. Rifampicin is bactericidal and inhibits mycobacterial RNA synthesis. Like INH, rifampicin also has excellent tissue penetration (including to the CNS). Rifampicin is excreted by the liver. It may be necessary to modify drug dosage in patients with hepatic disorders though not necessarily in renal failure. Rifampicin is usually given orally and the average daily dosage for adults is 600 mg given in the morning on an empty stomach. Rifampicin may also be a part of intermittent chemotherapy regimens; it is administered in two weekly doses of 600 mg. Patients taking rifampicin should be cautioned to expect orange discolouration of body secretions (urine, sweat, tears, and saliva). This manifestation has no clinical significance.[1] Rifampicin toxicity includes hepatitis, hypersensitivity reactions (characterised by fever, rash, and eosinophilia), and hematologic toxicity (thrombocytopenia, leukopenia, and hemolytic anemia). Hypersensitivity reactions are more common with intermittent therapy regimens. Rifampicin-induced hepatitis occurs in upto 10 per cent of patients and is characterised by nausea, vomiting and elevated AST levels.

Drug interactions are known to occur with rifampicin. Rifampicin potentiates the hepatotoxicity of INH (by accelerating its metabolism to hydrazine). Although the simultaneous administration of INH and rifampicin increases the risk of hepatotoxicity, the advantages of this excellent antimycobacterial combination outweighs this potential risk. Rifampicin antagonises the effect of warfarin, quinidine, and oral contraceptives.

Pyrazinamide: Pyrazinamide, a derivative of nicotinic acid, was initially tried as an antitubercular drug in the 1950s. The use of a high dose of the drug was associated with considerable toxicity at the time and this relegated the drug to the status of a second-line drug for years. Modification of the dose of the drug and recognition of its potent bactericidal effect, especially against dormant intracellular mycobacteria within the acid pH of the macrophages, led to a renewal of interest in this drug. Today pyrazinamide is an essential component of most short-course antituberculous regimens. Pyrazinamide is usually administered as a single oral dose of 15 to 30 mg/kg/day (to a maximum dose of 2 g). The drug is absorbed well and has excellent tissue penetration (including the CNS). Pyrazinamide is excreted by both hepatic and renal mechanisms. The major

[1] Damage to ocular contact lenses may occur.



Drug	*Extracellular/Rapidly multiplying*	*Slowly multiplying*	
		Acid pH (Intracellular)	*Neutral pH (Extracellular)*
Isoniazid	++	+	±
Rifampicin	++	+	+
Pyrazinamide	0	++	0
Streptomycin	+++	0	0
Ethambutol	±	±	0

Fig 8.8 Three populations of Mycobacteria in clinical lesions with drug susceptibility

Table 8.17 : Antitubercular drugs

Drug	*Adult dosage (daily)*	*Pediatric dosage (daily)*	*Main adverse effects*
First-line drugs			
Isoniazid (INH)	300 mg po,i.m.	10–20 mg/kg (max 300 mg)	Hepatic toxicity, peripheral neuropathy
Rifampin[1]	600 mg po,i.v.	10–20 mg/kg (max 600 mg)	Hepatic toxicity, flu-like syndrome
Pyrazinamide[2]	1.5–2.5 g po	15–30 mg/kg (max 2 g)	Arthralgias, hepatic toxicity, hyperuricemia
Ethambutol	15–25 mg/kg po	15–25 mg/kg PO	Optic neuritis
Streptomycin	15 mg/kg i.m.	20–30 mg/kg	Vestibular toxicity, renal damage
Second-line drugs			
Thiacetazone	150 mg PO	5 mg/kg	Gastrointestinal, skin reactions (Stevens-Johnson syndrome), hepatitis
Capreomycin	15 mg/kg i.m.	15–30 mg/kg	Auditory and vestibular toxicity, renal damage
Kanamycin	15 mg/kg i.m., i.v.	15–30 mg/kg	Auditory toxicity, renal damage
Amikacin	15 mg/kg i.m., i.v.	15–30 mg/kg	Auditory toxicity, renal damage
Cycloserine	250–500 mg bid po	10–20 mg/kg	Psychiatric symptoms, seizures
Ethionamide	250–500 mg bid po	15–20 mg/kg	Gastrointestinal and hepatic toxicity, hypothyroidism
Ciprofloxacin	500–750 mg bid po	Not recommended	Nausea, abdominal pain, restlessness, confusion
Ofloxacin	300–400 mg bid or 600–800 mg/day po	Not recommended	Nausea, abdominal pain, restlessness, confusion
Aminosalicylic acid (PAS)	4–6 g bid po	75 mg/kg bid	Gastrointestinal disturbance

[1] For intermittent use after a few weeks to months of daily therapy, dosage is 600 mg twice/week
[2] For intermittent use after a few weeks to months of daily therapy, dosage is 2.5 to 3.5 g twice/week

toxicities of the drug include hepatic dysfunction, hyperuricemia, and hypersensitivity.

Ethambutol: Ethambutol is only bacteriostatic against M. tuberculosis. It acts by interfering with the incorporation of mycolic acids into the mycobacterial cell wall. Ethambutol penetrates into tissue well, including those of the CNS when the meninges are inflamed. It is excreted principally by the kidneys. The drug dosage must be modified in patients with renal failure. Ethambutol is administered orally at an initial dose of 25 mg/kg/day for the first six to eight weeks of therapy, followed by 15 mg/kg/day for the rest of the course. The major toxicities of ethambutol include hypersensitivity reactions (fever and rash) and optic neuritis; the latter is dose-related and is usually first manifested by a loss of colour vision.

Streptomycin: Streptomycin is bactericidal against extracellular mycobacteria and acts by inhibiting mycobacterial protein synthesis. Tissue penetration of streptomycin is only fair; it penetrates the CSF poorly. Its excretion is principally renal and, therefore, dosage of the drug must be reduced in patients with renal failure. Streptomycin must be administered as an intramuscular injection. The adult dose is 15 mg/kg (maximum of 1 g) administered daily for two to eight weeks, followed by biweekly injections. Major toxicities include hypersensitivity reactions and vestibular toxicity (it damages the vestibular division of the cochlear nerve). Vertigo is indicative of vestibular toxicity.

Second-line antituberculous agents In addition to the five major drugs, several other agents are available for the treatment of tuberculosis (Table 8.17). These agents are used in infection with multiple drug-resistant mycobacteria.

Adjunctive therapy

Surgical treatment is rarely required for pulmonary tuberculosis. Indications include

1. resection of a large active cavity harboring drug resistant organisms, an aspergilloma or a bronchiectatic segment causing repeated hemoptysis;
2. complications such as a bronchopleural fistula; or
3. persistent tubercular empyema.

Corticosteroids may be used as adjunctive therapy when the patient is toxemic, or has an adult respiratory distress syndrome, tubercular pericarditis or adrenal insufficiency. They should be used for a short period (2–3 weeks) only.

Non-tuberculous (Atypical) Mycobacteria

This is a group of mycobacteria which differ from Mycobacterium tuberculosis in their microbiology, and treatment, although they can cause a disease similar to tuberculosis. These mycobacteria are commonly found in the soil, are not transmittable from person to person and exposure is more frequent than the development of the disease. Four categories are described based on the microbiology of the organisms, that is, their rate of growth and pigment production.[1]

Non-tuberculous mycobacteria cause a chronic insidious disease in patients with some form of local or systemic immunosuppression. The common disease causing organisms are M. kansasii, M. avium-intracellulare (MAI), M. xenopi, and M. scrofulaceum. These organisms cause pulmonary disease like tuberculosis. The less common mycobacteria M. fortuitum, M. chelonei, M. ulcerans and M. marinum usually infect soft tissues.

Non-tuberculous mycobacteria usually infect lungs already compromised by other diseases (prior tuberculosis, bronchiectasis and bronchitis). MAI infection is associated with HIV infection. Symptoms resemble pulmonary tuberculosis, and bacteriology must distinguish infection due to these organisms from tuberculosis. The chest X-ray shows confluent upper lobe shadows with cavitation; cavities tend to be *thin-walled* and *pleural effusions are rare.* Renal and skin lesions, cervical lymphadenitis and chronic osteomyelitis have been reported.

M. scrofulaceum causes granulomatous cervical lymphadenopathy in children. The disease is characterised by enlarged lymph nodes which may ulcerate, leading to sinus formation. M. marinum causes a granulomatous ulcerating skin lesion (swimming pool granuloma) and M. ulcerans causes chronic subcutaneous ulcers (Buruli ulcer). M. fortuitum causes injection site abscesses in drug addicts.

M. kansasii and M. xenopi infections respond to triple drug treatment with isoniazid,

1 The *photochromogens* (M. kansasii) require light to produce pigment, the scotochromogens (M. scrofulaceum) produce pigment independent of light, and the *nonchromogens* (M. avium-intracellulare) do not produce pigment. All these three types have a growth rate ranging from 10–21 days. The fourth group consists of rapid growers (growth rate 3–7 days, prototype M. fortuitum). This classification is called Runyon's classification. It is not generally used clinically as it does not classify M. tuberculosis or M. leprae.

rifampicin and ethambutol for upto one year. The MAI complex is poorly responsive to drugs. A combination of ethambutol, rifampicin, ciprofloxacin and clarithromycin (or clofazimine) may be effective but treatment must be continued for two years. Surgical excision may be required for cutaneous infection due to non-tubercular mycobacteria.

Leprosy (Hansen's disease)

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae.* The disease affects the skin and peripheral nerves principally, although it can occasionally involve multiple organ systems.

Epidemiology It is estimated that there are 5.5 million cases of leprosy worldwide. The greatest concentration of cases is in south-east Asia, particularly in India where there were 1.9 million registered cases in 1991. The overall prevalence rate in south-east Asia is estimated to be 20.5 cases per 10,000.

Microbiology *Mycobacterium leprae* is an acid-alcohol fast obligate intracellular parasite that has *phenolic glycolipids* as a prominent cellular constituent and which resides within monocytes, tissue macrophages and Schwann cells in peripheral nerves. It has an unexplained tropism for Schwann cells which is responsible for the characteristic nerve damage and its preference for ambient temperatures below 37°C (which accounts for its selective growth in cooler parts of the body such as the skin, nasal mucosa and the testes) The organism has not been grown on artificial media or in tissue culture. Besides human beings, the lepra bacillus can infect only the nine-banded armadillos and the sooty mangabey monkeys. The incubation period of leprosy ranges from five to fifteen years, which is a reflection of the very slow replication of the organism. Patients may, therefore, be infective for years prior to the clinical diagnosis and they serve as a reservoir of infection within the community in an endemic area. *Mycobacterium leprae* is present in the nasal secretions and is transmitted by respiratory droplets. In endemic tropical areas, 95 per cent of infected individuals mount an effective immune response and do not develop clinical disease. In subjects who do go on to develop clinical disease, the nature of the host immune response determines the clinical pattern of disease. Immunologically, pathologically, and clinically, leprosy is characterised by a spectrum of features that extend from two polar forms to intermediate stages. In the tuberculoid form of the disease, a good cellular immune response limits the intracellular multiplication of the organism and the disease is confined to a few skin patches or selected nerve trunks. Histologically, this form is characterised by infiltration of CD_4^+ T lymphocytes[1] and granuloma formation within the dermis of the skin and the perineurium of involved nerves. There are few if any acid-fast bacilli within the lesions. The other correlates of this form of the disease are a strong skin test reactivity after the intradermal injection of killed *M. leprae* (*lepromin test*[2]) and the in vitro production of lymphokines (including interferon production by antigen specific CD_4^+ lymphocytes). The other polar form of the disease is *lepromatous leprosy* which is characterised by the absence of specific cellular immunity to the organism; uncontrolled proliferation of the bacilli results in extensive skin lesions and dermal nerve destruction. Histologically, this form features an infiltrate of macrophages laden with bacilli (globii) – the *foam cells* – with scanty lymphocytes which, include both CD_4^+ and CD_8^+ phenotypes. Though the cellular response is weak, there is a strong humoral antibody response to the mycobacterial antigens. Between

[1] CD_4^+ cells are T helper cells.

[2] The lepromin reaction is an indicator of the ability of the host to mount a cell-mediated immune response to Mycobacterium leprae. An early reaction occurs at 48 hours (Fernandez reaction) and a delayed reaction (Mitsuda reaction) occurs at 3–4 weeks. The late reaction correlates most consistently with the immune status.

these two polar forms, there are several intermediate forms (Table 8.18).

The polar forms are relatively stable whereas the intermediate forms may 'upgrade' or 'downgrade' to another form. A form of leprosy unique to the Indian subcontinent is pure *neuritic leprosy* without skin lesions.

Clinical features *Tuberculoid leprosy* is characterised by two to three maculoanesthetic[1] lesions that have hypopigmented scaly centres, are devoid of hair, have sharp raised erythematous borders and are associated with palpable cutaneous nerves. Nerve and cutaneous involvement is typically asymmetric.

Lepromatous leprosy in its earliest form presents as 'juvenile leprosy'. In this *prelepromatous stage* skin involvement is subtle; the skin texture is not appreciably changed. There are vague macules with indistinct borders that are seen only under appropriate lighting. There are no alterations in superficial sensation or sweating. Acid-fast bacilli are seen only infrequently in the smears from the skin. As the disease progresses, the skin involvement is characterised by symmetrically distributed macules, papules, plaques and nodules (*lepromas*) over wide areas of the skin. Often there may be no discrete lesion but the skin looks shiny and raised. Loss of the outer third of eyebrows and eyelashes is not uncommon. The involvement of the face with lepromas can lead to *leonine facies.* The ears and earlobes are frequently involved and the latter may appear thick and pendulous. Paralysis of the zygomatic branch of the facial nerve can lead to *lagophthalmos*[2] and this may also be associated with corneal anesthesia. Ocular involvement may occur and lead to the formation of conjunctival and episcleral nodules. With involvement of the cornea, there may be beading of corneal nerves, and the development of a superficial *punctate keratitis* or an interstitial keratitis with *pannus formation.* Eventually a chronic *plastic iridocyclitis* develops and can result in blindness; indeed leprosy is an important preventable and treatable cause of blindness in endemic areas. Infiltration of the mucous membranes of the upper respiratory tract manifests as nasal stuffiness, coryza and epistaxis. Nasal cartilage involvement can lead to septal destruction and a saddle nose. Oropharyngeal infiltration can lead to ulcers of the uvula, tonsils and even loss of teeth. Laryngeal infiltration in advanced cases can lead to hoarseness of the voice, stridor and even asphyxia. Systemic involvement may lead to hepatomegaly, splenomegaly and rarely, lymphadenopathy. Testicular involvement and destruction can lead to gynecomastia. Renal involvement in lepromatous leprosy takes the form of an *immune complex nephritis,* or proteinuria of a varying degree secondary to *renal amyloidosis.*

Borderline leprosy, sometimes also called dimorphous or *intermediate leprosy,* is an unstable form of the disease. It may evolve towards the tuberculoid form by reversal reactions or downgrade towards lepromatous disease. Borderline leprosy patients are particularly prone to major damage to the nerves, often early in the disease. Involvement of the peripheral nerves leads to their enlargement, motor weakness and sensory disturbances. Motor weakness leads to typical deformities depending on which nerve is involved (Table 8.19). Damage to the dermal nerves can cause a '*glove and stocking*' anesthesia, in addition to the involvement of nerve trunks. Anesthesia in the distribution of the nerves results in trophic changes and a propensity to chronic ulceration from repeated trauma. The underlying bone may become infected (*osteomyelitis*), and cystic changes in the distal phalanges have been described. The joints may be deformed in leprosy secondary to denervation (*neuropathic joints*[3]).

[1] Macular lesions which are also anesthetic are called maculoanesthetic.

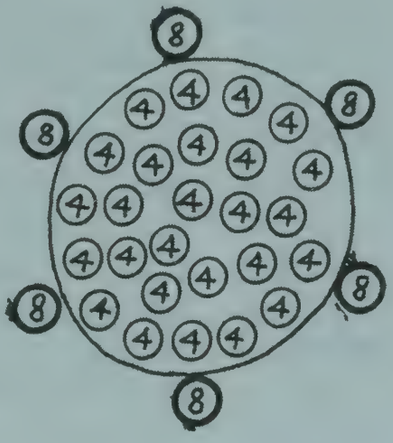
[2] Lagophthalmos refers to the inability to close the eyes (like the eyes of a hare).

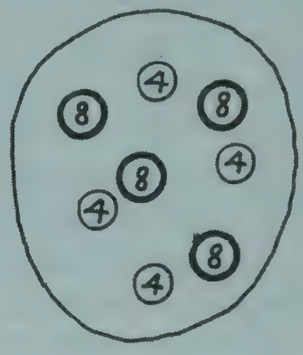
[3] Also called Charcot's joints. These are not specific to leprosy but are also found in neurosyphilis, diabetes and syringomyelia.

Table 8.18 Characteristics of the immunological spectrum of leprosy

Characteristic/stage :	*TT*	*BT*	*BB*	*BL*	*LL*
Bacilli in lesions	±	±/+	+	++	+++
Bacilli in nasal discharge	–	–	–	+	+++
Granuloma formation	+++	++	+	–	–
In vitro correlates of CMI	+++	++	+	±	–
Reaction to lepromin	+++	+	–	–	–
Anti *M. leprae* antibodies	+	±	+	++	+++
Clear subepithelial zone in skin biopsy	++	±	–	–	– –
Macrophage maturity	Mature				Immature
Duration of therapy	short (6 months)				long (2 years)

Immunohistopathology
④ = T_4 = T helper cells
⑧ = T_8 = T suppressor cells
TT = tuberculoid
BT = borderline tuberculoid
BB = borderline
BL = borderline lepromatous
LL = lepromatous





Patients with intermediate forms of leprosy may in addition experience two types of clinical reactions. *Type 1* or reversal reactions are characterised by a spontaneous increase in the cellular immune response to mycobacterial antigens in the skin and the nerves due to infiltration of T cells into these sites. Reversal reactions may be seen in about 30 per cent of patients with *borderline leprosy*. The skin lesions become erythematous and there is acute painful neuritis. These reactions are a major contributor to nerve damage in patients with tuberculoid and borderline leprosy. *Type II* reactions are also called *erythema nodosum leprosum* and affect patients with *borderline lepromatous* and *lepromatous leprosy* who have a large bacillary load. The patients develop tender cutaneous nodules and other systemic features such as fever, arthralgia and myalgia. The release of the lymphokine *tumour necrosis factor* and vasculitis of dermal arteries and veins are believed to be the mechanisms responsible for these reactions. *Neuritis, glomerulonephritis and orchitis* may occur as part of a widespread deposition of the immune complexes consisting of mycobacterial antigens and antibodies.

Diagnosis The key to the proper diagnosis of early leprosy is the careful sensory examination of all hypopigmented macules. Regional

Table 8.19 Peripheral nerve involvement in leprosy*

Nerve	*Site of enlargement*	*Clinical sequelae*
Ulnar	elbow, near the medial aspect of the olecranon process	wasting of small muscles of hand; clawing of 4th and 5th fingers
Posterior tibial	between the medial malleolus and heel	clawing of toes, plantar anesthesia
Superficial peroneal	near the neck of fibula	foot drop
Greater auricular	crossing the sternomastoid in the neck	cosmetic
Median	antecubital fossa; proximal to carpal tunnel at wrist	thenar wasting; palmar anesthesia
Radial	near radius at the wrist	wrist drop (unusual)
Facial	stylomastoid foramen; zygomatic process	lagophthalmos
Trigeminal	near corresponding foramina	facial, corneal and conjunctival anesthesia

* in approximate descending order of frequency of clinical involvement

variations in the richness of dermal nerve supply must be kept in mind; there must be extensive damage to dermal nerves in the face before sensory changes can be detected whereas the skin over the knees, elbows, and greater trochanters is normally mildly hypoesthetic. Touch is tested with the use of a few cotton fibres or a fine nylon thread and heat-cold discrimination is tested by using test tubes with warm and cold water. The main nerve trunks must be carefully palpated for thickening, enlargement and tenderness and the skin adjacent to the cutaneous lesions palpated for enlarged cutaneous nerves. It must be borne in mind that leprosy is probably the most common cause of peripheral neuropathy in the world.

Skin smears for acid-fast bacilli are usually taken from the earlobes or from the edge of the macules or plaques. A fold of skin is pinched between the thumb and the forefinger and a short, shallow slit is made in the skin with a scalpel blade. The edge of the blade is then turned at right angles to the slit and the edge of the incision is scraped lightly. The cells and the fluid so obtained are spread on a slide and stained by the routine *Ziehl-Nielsen* method used to demonstrate mycobacteria. On occasion, a biopsy of the skin may be required to establish the diagnosis; tissue mycobacteria are better stained with the *Fite-Faraco* stain.

Treatment For the purpose of treatment, the tuberculoid forms of the disease (TT and BT) are classified as *paucibacillary* leprosy. These patients usually have a bacillary load of less than 10^6 organisms and are unlikely to harbour drug-resistant mutants. They can be treated adequtely for a limited period with two drugs. The polar lepromatous forms are classified as *multibacillary* leprosy. These patients may be infected with over 10^{12} organisms and require prolonged treatment with three antileprosy drugs to prevent the development of drug-resistant strains of *M. leprae.*

The multidrug regimens approved by the WHO are shown in Table 8.20. A crucial component of these regimens is the monthly supervised administration of a dose of *rifampicin,* which has a bactericidal effect on 99.9% of the viable bacilli. *Dapsone,* a sulfone compound, is bacteriostatic for *M. leprae* and had been the mainstay of leprosy therapy till resistance to it became frequent. The drug interferes with mycobacterial purine bisynthesis due to its sulfonamide-like effect on folate metabolism. Side effects of the dapsone therapy

Table 8.20 Multidrug therapy for leprosy

	Paucibacillary	*Multibacillary*
Disease type	Tuberculoid forms (TT, BT)	Lepromatous forms (BB, BL, LL)
Monthly	Rifampicin (600 mg) -supervised	Rifampicin (600 mg) + Clofazimine (300 mg) -both supervised
Daily	Dapsone (100 mg) -self administered	Dapsone (100 mg) + clofazimine (50 mg) -self administered
Period of treatment	Six months	Two years or longer (until skin smears are negative for acid fast bacilli)

are infrequent and include nausea, vomiting, rash, transient headaches, hemolysis and meth-hemoglobine-mia. *Clofazimine,* a phenazine derivative, is bactericidal for *M. leprae* due to its binding to mycobacterial DNA. Side effects include dose-related gastrointestinal symptoms such as pain, nausea and vomiting (related to segmental deposition in the small intestinal wall) and anticholinergic symptoms. A reddish to dark brown discolouration of the skin (often accompanied by icthyosis[1] and related to the lipophilicity of the drug), comea, and all body fluids is a troublesome side effect that may take months or even years, to disappear, after the drug is discontinued.

Reversal reactions require prolonged treatment with immunosuppressive doses of prednisone (40–60 mg/day) for three to six months. Episodes of *erythema nodosum leprosum* are treated with shorter courses of steroids. Clofazimine has an important role in the management of these reactions due to its anti-inflammatory effect. The drug *thalidomide* is highly effective in treating these reactions as it can inhibit the release of *tumour necrosis factor* from the activated macrophages. A major problem in the use of thalidomide, besides its teratogenicity, has been the restricted availability of the drug in countries where leprosy is endemic.

[1] Icthyosis refers to scaly, rough, dry fish-like skin.

Health education is an important component of management of these patients. They are taught to care for their anesthetic hands and feet to prevent further damage. Paramedical personnel are taught to manage recurrent ulcers of hands and feet to which these patients are particularly prone. Specialised surgery has a limited role in our country; muscle imbalance can be corrected by the transfer of tendons. The rehabilitation of subjects with established nerve damage with a view to decreasing functional impairment is very important.

Leprosy control

The key to leprosy control in the tropics is the implementation of the multidrug treatment programmes and active case finding. Community education and reducing the social stigma attached to the disease will go a long way towards *self-presentation.* Early treatment not only limits disability but also reduces the bacillary load in the community. The efficacy of the BCG vaccination in the prevention of leprosy has varied from 20–80 per cent in different clinical trials. It is believed that the BCG vaccination is more effective in controlling leprosy than tuberculosis because *Mycobacterium bovis (Bacille Calmette et Guerin, BCG)* has a greater structural similarity to *M. leprae* than to *M. tuberculosis.*

KEY CONCEPTS

Streptococcus

- Group A (*β hemolytic*) streptococci are the most virulent; they cause pharyngotonsillitis (tonsillar exudate with tender cervical lymphadenopathy), pneumonia, rheumatic fever, scarlet fever, cellulitis, erysipelas, impetigo and wound infections. A carrier state is well-recognised.
- Group D (*enterococci*) cause urinary tract infection, intraabdominal sepsis and endocarditis. Group B streptococci cause neonatal sepsis and puerperal infections. Non-typable (*viridans*) streptococci cause dental caries, subacute endocarditis and suppurative infections of brain and abdominal viscera.
- Diagnosis is with Gram stain of smear, culture of blood/exudate; ASLO and other antibodies provide supportive evidence.
- Penicillin is the drug of choice for infections with Group A/B and untypable strains. A ten day course must be completed in patients with pharyngitis. Erythromycin may be used in patients with penicillin allergy. Enterococci are best treated with a combination of a penicillin and an aminoglycoside.

Staphylococcus

- These are ubiquitous organisms carried on the skin and in the anterior nares; newborns, patients with chronic obstructive pulmonary disease, influenza, intravascular catheters or an immunosuppressed state are especially prone to infection
  - Skin infections include furuncles, impetigo, carbuncles and the scalded skin syndrome (Phage type II)
  - Staphylococcal pneumonia principally affects infants and the elderly. The formation of a pneumatocele, abscess, or an empyema is typical.
  - Staphylococcal endocarditis is a consequence of staphylococcal bacteremia. The clinical presentation is acute with a tendency for the formation of valve ring abscesses. The illness is associated with a high morbidity and mortality.
  - Staphylococcal enterocolitis is an invasive colitis that afflicts patients with depleted indigenous intestinal flora (such as due to antibiotic treatment).
  - Staphylococcal food poisoning is a self-resolving illness due to a preformed enterotoxin. The illness has an incubation period of 2–8 hours and is characterised by nausea and vomiting.
  - Toxic shock syndrome: toxigenic strains (Phage type 1) produce a syndrome of fever, vomiting, an erythematous rash and shock. It was originally described in women who were using contaminated tampons.
- The diagnosis of staphylococcal infection requires demonstration of organisms on Gram stain of exudate, or in blood cultures.
- Management consists of drainage of the abscess (where necessary and feasible) and antibiotic treatment with a penicillinase-resistant penicillin; hospital strains of methicillin-resistant staphylococcus aureus respond best to vancomycin/cotrimoxazole.

Pneumococcus

- Patients with lymphomas, myeloma, sickle cell disease, splenectomy or immunodeficiency states are especially prone.
- Lobar pneumonia is the most common manifestation in adults. Pneumococcus is one of the most common causes of otitis media in infants and bacterial meningitis (all ages). Patients with nephrotic syndrome and cirrhosis are predisposed to develop pneumococcal peritonitis.
- Diagnosis is by Gram stain and culture of sputum, exudate and CSF. Blood cultures may be positive in bacteremic illness.
- Penicillin G is the drug of choice; if penicillin resistance is suspected, vancomycin may be used.
- Polyvalent pneumococcal vaccine may be considered for the elderly, and in patients with asplenia or COPD.

Meningococci

- *Neisseria meningitidis* resides on the nasopharyngeal mucosa. The peak incidence of infections is in the first two years of life and in children.
- Meningococcemia and meningitis are two clinical syndromes. Meningococcemia manifests with fever, petechial rash and, on occasion, shock (*Waterhouse-Friderichsen syndrome*). Bacteremia may be associated with pericarditis and arthritis. Meningitis presents with fever, headache and neck stiffness; cranial nerve palsies are a frequent residue.
- Diagnosis is by isolating the organism from blood, CSF or joint fluid.
- Treatment consists of parenteral penicillin, third-generation cephalosporin/chloramphenicol. Contacts should receive prophylaxis with rifampicin.

Hemophilus influenzae

- Capsulated Type B is the most virulent and causes most bacteremic disease. Children are affected more often than adults.

- The spectrum of illnesses includes life-threatening epiglottitis, otitis media, facial cellulitis, septic arthritis and meningitis (with high incidence of residual deficits) in children. In adults pneumonia and tracheobronchitis are more common; elderly patients with COPD, alcoholism and head injury are more prone.
- The diagnosis is by Gram stain and the clinical picture; the organism is frequently present in the sputum of COPD patients without indicating infection.
- Bacteremic illness is treated with parenteral ampicillin and chloramphenicol (or third-generation cephalosporin); endocarditis is treated with i.v. ampicillin with an aminoglycoside; non-bacteremic illness can be treated with ampicillin (or cephalosporin/quinolone) alone.

Enteric fever

- Febrile systemic illness is due to S. *typhi, S. paratyphi A and B.* Water- or food-borne illness is endemic in the tropics; raw vegetables are a source.
- The ingested organisms multiply in the intestinal Peyer's patches, followed by systemic bacillemia.
- The clinical features include high fever (usually remittent; a *step ladder pattern* is classical but uncommon), cough followed by prominent abdominal complaints (usually constipation followed by diarrhea). Signs include coated tongue, relative bradycardia (classical but uncommon), hepatomegaly, splenomegaly, and *Rose spots* (uncommon in dark-skinned).
- Complications include GI hemorrhage and perforation; encephalopathy is seen in children.
- There is laboratory evidence of leucopenia. Blood and bone marrow cultures are positive in first 2 weeks; urine and stools cultures become positive subsequently. A serologic test (*Widal*) is useful and moderately sensitive but lacks specificity; it differentiates typhoid from paratyphoid.
- Chloramphenicol was the traditional drug of choice. Ampicillin/amoxycillin too are effective. The treatment course lasts 14 days. Ceftriaxone and oral fluoroquinolones are emerging as alternative treatments in areas with a high prevalence of antibiotic resistant strains. Glucocorticoids have an important adjunctive role in lowering mortality in typhoid encephalopathy, and in hypotensive patients. Avoid aspirin as an antipyretic. Relapses occur in 10 per cent.

Shigellosis

- It is transmitted by the feco-oral spread of organisms in contaminated food and water, and is endemic in tropics.
- The clinical picture is variable: fever, abdominal cramps, tenesmus, diarrhea to severe dysentery. The complications include dehydration, hemolytic-uremic syndrome, post-dysenteric reactive arthritis.
- Stool examination reveals leucocytes (which suggests invasive colitis); bacteriologic proof requires smear and culture of rectal swab.
- The treatment consists of oral or i.v. rehydration along with either trimethoprim-sulphamethoxazole combination or a quinolone (for 5 days).
- Washing hands after defecation and good sanitation are essential.

Cholera

- This is a water-borne disease endemic in tropical areas with poor sanitation. *El Tor* biotype causes milder disease compared to the *classical* biotype.
- The cholera enterotoxin causes secretory diarrhea with isotonic loss of fluid by stimulating adenyl cyclase within luminal gut cells.
- Clinical features include *rice water* stools with diarrhea, moderate to severe dehydration, oliguria, and hypotension. Complications include shock and acute renal failure.
- *Hanging drop* preparation or dark ground illumination can identify the curved motile organism. Specific antiserum is available for agglutination test.
- The treatment consists of oral replacement of fluid deficit with glucose-electrolyte solutions. Early treatment with tetracycline (for 2 days) and single dose doxycycline reduce the stool volume and duration of diarrhea.
- Carriers should be treated with ampicillin (with probenecid)/cotrimoxazole, and cholecystectomy (if gallbladder disease is present).

Plague

- This is a flea-borne illness due to *Yersinia pestis;* rodents are vectors.
- The *bubonic* type is the most common and is characterised by local eschar followed by high fever, enlarged tender lymph nodes (*buboes*) in the neck, groin or axillae. Associated hepatosplenomegaly and fever are seen.
- The *pneumonic* type is characterised by cough, fever, streaking of sputum, tachypnea and roentgenographic evidence of a rapidly progressive pneumonia.
- The *septicemic* type presents with GI symptoms, DIC and purpura.
- Diagnosis is by recovery of the organism (bipolar 'safety pin' appearance) from blood, sputum or lymph node aspirate; serologic tests available.

- Streptomycin (for 10 days) is the drug of choice; chloramphenicol is an alternative.
- Prevention includes prophylaxis of contacts with tetracycline (for 6 days), and pest control.

Gas gangrene

- There is progressive myonecrosis due to *Clostridium perfringens.*
- Contamination of the wound with the organism and the presence of a low redox potential are prerequisites. The disease is heralded by progressive pain, tenderness and edema of the involved muscles. The presence of gas in tissues results in *crepitus.* The patient appears toxic, and renal failure may be a complication.
- Stain and culture of the wound exudate establish diagnosis.
- The treatment consists of wound debridement and drainage and antibiotics (penicillin). Hyperbaric oxygen and anti-gas gangrene serum are of doubtful efficacy.

Tetanus

- C.tetani is a ubiquitous anerobe that causes disease due to wound contamination. *Tetanospasmin* produced locally by the organism travel to the CNS (via the peripheral nerves) where it interferes with the function of spinal inhibitory neurons.
- Its hallmark is sustained contraction of agonist and antagonist groups of muscles (*tetanic contraction*). Jaw spasm, neck stiffness and arched hyperextended back are common features. The spasm can cause apnea and fluctuation in BP.
- The diagnosis is clinical. Treatment consists of i.v. administration of tetanus immunoglobulin along with tetanus toxoid (opposite arm). Other important components of management include wound care (debridement; penicillin), sedation, relief of spasm (with benzodiazepines and neuromuscular blockade), and supportive measures (ventilatory support, alimentation, fluid balance).

Botulism

- The disease is caused by ingestion of preformed neurotoxin in food contaminated with the anerobe.
- The toxin inhibits the release of acetylcholine resulting in brainstem neuronal dysfunction. Symptoms of ocular and bulbar muscle weakness, along with skeletal and respiratory muscle paresis dominate the clinical picture.
- The diagnosis is clinical; food may be examined for organism/toxin.
- Treatment consists of ventilatory support and antitoxin.

Tuberculosis

- The term refers to *disease* (not *infection*) due to Mycobacterium tuberculosis. The infection is acquired by the inhalation of droplet nuclei.
- Exposure is very common in the tropics but disease develops only in 5–15% of those with infection. *Primary* tuberculosis refers to the initial pulmonary response to infection which is most often subclinical; a primary focus (*Ghon's*) is formed that heals without sequelae.
- Most clinical tuberculosis is either due to *exogenous reinfection* or due to *reactivation.*
- *Pulmonary* tuberculosis manifests with fever, night sweats, malaise, cough and hemoptysis.
- *Extrapulmonary* disease is usually the result of dissemination from a pulmonary focus. Manifestations include lymph node tuberculosis (scrofula); pleurisy with effusion; pericarditis with effusion/constriction; gastrointestinal disease : granulomatous hepatitis, ileocecal disease, mesenteric lymphadenitis, peritoneal tuberculosis; genitourinary tuberculosis: chronic salpingitis, endometritis with amenorrhea, infertility ; osteoarticular tuberculosis (Pott's spine) and CNS infection (chronic basilar meningitis, tuberculoma, infarcts due to endarteritis). Miliary tuberculosis manifests with non-specific symptoms, severe toxicity, choroidal tubercles, and with interstitial infiltrates on the chest X-ray.
- Investigations for pulmonary tuberculosis include a chest X-ray (upper lobe infiltration with or without cavitation is typical) and sputum for acid-fast bacilli (at least 3 examinations). A gastric lavage may be required if patient is swallowing sputum. For extrapulmonary tuberculosis, investigations are targeted at the system involved (lymph node aspiration/biopsy, bone X-ray, endometrial biopsy, liver biopsy, CT scan, CSF examination).
- Management currently emphasises *directly observed treatment* using *short course chemotherapy.* INH, rifampicin, pyrazinamide and ethambutol/streptomycin are initially administered for 12 weeks, INH and rifampicin are then continued for another 6 months. Extrapulmonary tuberculosis may require a longer period of treatment.
- Clinical and bacteriologic markers are used to assess response; sputum becomes negative for acid within fast bacilli 3 months. Liver function tests are obtained periodically to monitor drug toxicity. Steroids have an important adjunctive role in tubercular pericarditis (reduce constriction), meningitis (reduce cerebral edema), and miliary tuberculosis (reduce toxemia).

Leprosy

- Chronic granulomatous disease with a long incubation period (3–5 years) due to Mycobacterium leprae.
- There is a spectrum of illness: *tuberculoid* (TT: hypopigmented maculoanaesthetic patches; low bacillary load; intense cellular response) and *lepromatous* (LL: nodular infiltrates; high bacillary loads; foam cells with *globii*, no detectable CMI). *Borderline* lesions (BB, BT, BL) have intermediate characteristics.
- Peripheral nerve involvement is a constant feature irrespective of the type of skin lesions. *Pure neuritic forms* are recognised in India: the greater auricular nerve in the neck, ulnar nerve at the elbow and peroneal nerve at the fibular head are typically affected. There is a palpable, thickened nerve with sensorimotor loss in the nerve distribution.
- *Reactions* are common in leprosy. Type 1 or *reversal* reactions manifest with worsening of basal lesions and a shift to tuberculoid form concomitant with an increase in CMI. Type 2 reactions (*erythema nodosum leprosum*) occur in the lepromatous form of disease; an Arthus reaction results in fever, arthralgia, and subcutaneous nodules in crops.
- Diagnosis of the disease is confirmed by 'slit and smear' examination of infiltrated lesions, skin biopsy or, on occasion, nerve biopsy.
- *Paucibacillary disease* (TT/BT: $<10^6$ organisms) is treated with daily dapsone + monthly rifampicin for 6–12 months; *multibacillary disease* (LL/BL/BB; 10^{12} organisms) is treated with daily dapsone and clofazimine along with monthly rifampicin and clofazimine for at least two years.

8.6 Sexually transmitted diseases

Sexually transmitted diseases (STD) are infections for which sexual transmission is epidemiologically significant. It follows, therefore, that sexual transmission may not be the only way by which these infections are acquired. The contribution of non-venereal transmission mechanisms varies depending on the particular infection. Two observations are of specific epidemiologic concern with regard to sexually transmitted diseases. One is the recognition of the presence of a population at high risk for disease, who do not come to the physician but who nevertheless can be contacted, that is, the already infected, or potentially susceptible sexual partners of the patient who presents to the physician. The other observation is the frequent concomitant prevalence of more than one infection in a given patient. The implication for the physician is that since promiscuity and a high degree of sexual activity (including multiplicity of partners) are often central to the acquisition of sexually transmitted diseases, the patients presenting with one STD must be screened for the presence of other concomitant infections. The physician must also counsel patients appropriately about the potential for future reinfection, along with advice about specific preventive methods.

Cutaneous inoculation during sexual contact is the most common route of transmission of syphilis, gonorrhea, chlamydia, chancroid, herpes simplex and granuloma inguinale. HIV, hepatitis B and cytomegalovirus are examples of infections transmitted by blood products as well as by sexual means. Only the first group of disorders is discussed in this section (the latter group of disorders is discussed separately).

Sexually transmitted diseases can manifest as one of four syndromes: vaginitis, urethritis, genital ulcers (often with lymphadenopathy), or as localised growths. These are discussed below.

DISORDERS MANIFESTING AS VAGINITIS

Women with vaginal discharge often seek gynecological attention. Nevertheless, since the agents which cause vaginitis are few and clinical distinction relatively easy, the primary care physician can treat most of these infections thereby avoiding unnecessary referrals. The differential diagnosis of vaginal discharge and the specific organism-based treatment are summarised in Table 8.21.

DISORDERS MANIFESTING AS URETHRITIS

Urethritis usually presents with the presence of an exudate in the anterior urethra, often associated with a history of dysuria or urethral discomfort. The usual clinical approach is displayed in Fig 8.9 and the two common conditions, that is, gonococcal and non gonococcal infections, are discussed below.

Gonococcal Urethritis

Gonorrhea is an acute infection of the epithelium of the urethra, cervix, rectum

Table 8.21 Differential diagnosis of vaginitis

	Yeast vaginitis	*Trichomonal vaginitis*	*Bacterial vaginosis*
Organism	*Candida albicans*	*Trichomonas vaginalis*	*Gardenella vaginalis*
Clinical features			
1. Discharge characteristics	white curd, scanty	yellow-green profuse, frothy	grey, moderate
2. Pruritus	+++	+++	+
3. Odour	+	+	++
4. pH*	4.2 – 5.0	5.5 – 5.8	5.0– 5.5
Microscopy	pseudohyphae	motile flagellated parasite, neutrophils	squamous epithelial cells stippled with gram-negative bacteria (*clue cells*)
Treatment	miconazole (200 mg) or clotrimazole (100 mg) (1-2 tablets every day for 3 days)	metronidazole (2 g single dose)	metronidazole (0.5 g bd × 7 days)

* normal pH of vaginal fluid = 3.8 – 4.2

pharynx or conjunctiva that is caused by Neisseria gonorrhoeae.

Microbiology Neisseria gonorrhoeae is the causative agent of gonorrhea. Neisseria occurs as gram-negative encapsulated piliated kidney-shaped intracellular diplococci that lie with their adjacent surfaces concave.

Pathogenesis Gonococci attach to the mucosal cells aided by their pili and the microbial production of an IgA protease that counters local mucosal immunity. The capsule is a virulence factor. If the infection is due to a particular auxotype[1] or if serum complement components (C5,6,7,8) are deficient, then there is a predisposition to disseminated infection.

[1] Biotype based on the requirement for nutrients on agar plates; the arginine$^-$, hyoxanthine$^-$, uracil$^-$ strains cause disseminated infection

Epidemiology Gonorrhea is a disease of sexually active young men and women. Commercial sex workers are particularly at risk as are individuals with multiple sexual partners. The risk of acquiring infection after contact with an infected partner is higher in women (50%) than in men (20%).

Clinical features The clinical features of gonorrhea can be divided into genital and extragenital infections and these two categories are discussed separately.

Genital gonococcal infection

The primary site of genital gonococcal infection is the anterior urethra in men and the endocervical mucosa in women. Men present with a history of a purulent urethral discharge, often associated with moderate to severe dysuria, about 2–7 days after sexual contact with an infected partner. With the spread of infection

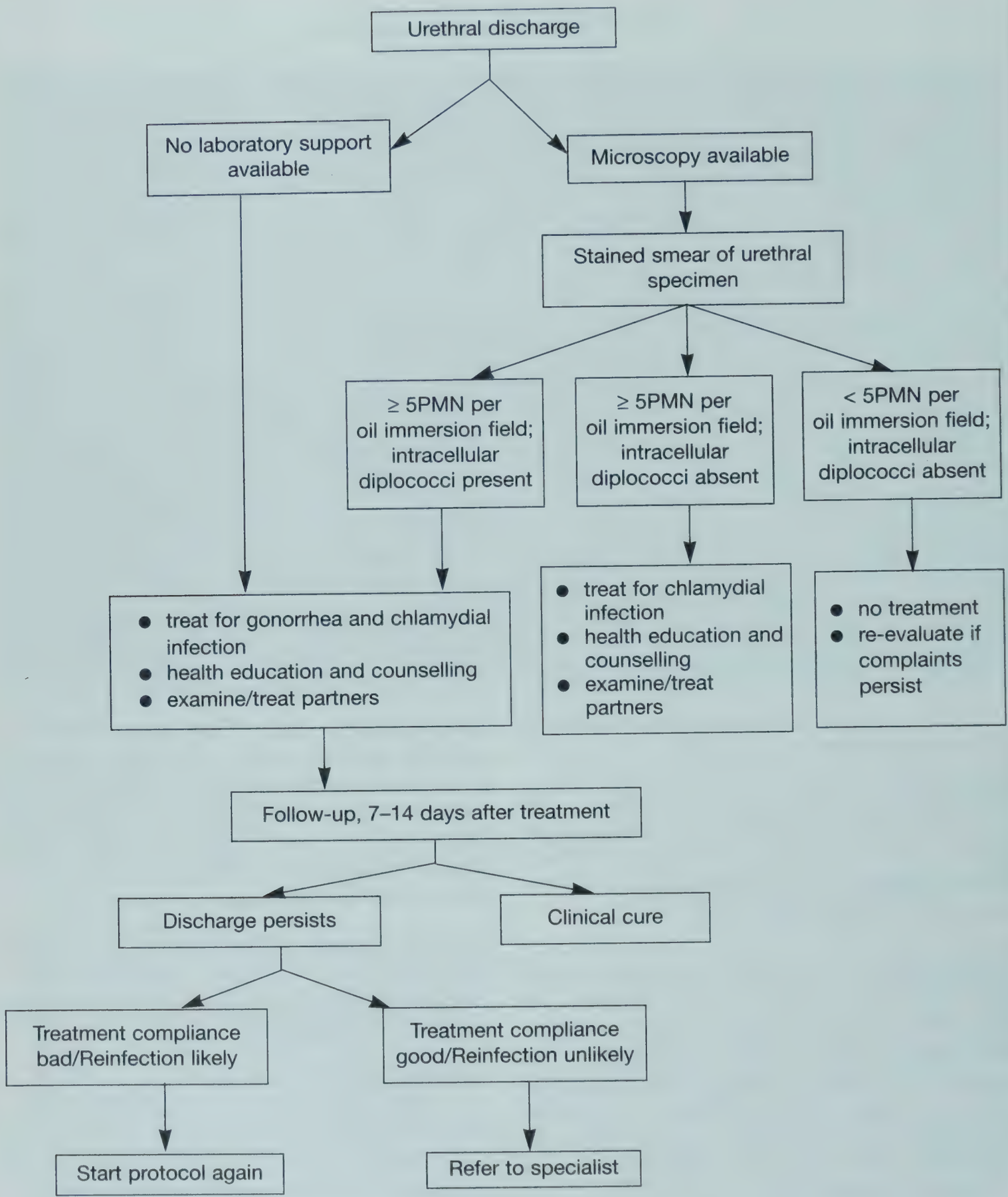


Fig 8.9 Algorithm for the management of urethritis
(Modified from WHO Technical Report Series 810; 1991)

PMN = Polymorphonuclear cells

o the posterior urethra, frequency and urgency of micturition may supervene. On examination he lips of the meatus may be swollen and red. If ıntreated, dysuria may subside but the purulent lischarge persists as 'gleet'. Uncommon complications include acute epididymitis, prostatitis and, later on, the development of a ırethral stricture. Unlike men, the majority of vomen with gonococcal cervicitis tend to be ısymptomatic or complain of a copious vaginal lischarge with only mild symptoms. The nfection may spread to adjoining structures such ıs Skene's glands or Bartholin's glands. Women vith gonorrhea often become more symptomatic vhen pelvic inflammatory disease (PID) levelops as a complication. PID often begins vith the onset of menstruation and manifests as ndometritis (midline abdominal pain), alpingitis (bilateral lower abdominal liscomfort) or as pelvic peritonitis (fever, eucocytosis, cervical motion tenderness, and ilateral adnexal tenderness). Salpingitis can esult in tubal occlusion and may cause ectopic pregnancy or sterility.

Extragenital gonococcal infection

Disseminated gonococcal infection, also called the *arthritis-dermatitis syndrome,* occurs more often in women, usually in the perimenstrual period. The genital infection is usually asymptomatic. Gonococcal bacteremia results in fever, malaise, migratory polyarthralgia or polyarthritis and a skin rash; the rash consists of crops of petechial or pustular lesions most often on the periphery of the limbs. A particularly common problem is the development of painful tenosynovitis. In the second week of the illness, the arthritis tends to become localised to a single joint and skin lesions are scant and discovered by careful examination around the joints.

Gonococcal perihepatitis (*Fitz-Hugh-Curtis syndrome*) is often seen in patients with disseminated infection. Right upper quadrant pain or the presence of a hepatic friction rub are clues to the disorder. Sometimes the pain can be severe enough to mimic cholecystitis.

The uncommon extragenital manifestations of gonococcal infection include pharyngitis (seen in individuals indulging in oral sex), endocarditis

Table 8.22 Treatment of gonorrhea

Category	*Primary regimen*	*Alternative regimen*
Gonorrhea (urethritis, cervicitis) in men and non-pregnant women	Ceftriaxone 250 mg i.m. + Doxycycline 100 mg twice daily x 7 days	Doxycycline 100 mg twice daily x 7 days + Spectinomycin 2.0 g i.m./Ciprofloxacin 500 mg oral single dose/ Ampicillin 2 g + probenecid 1 g oral (if penicillin resistance is not of concern)
Gonorrhea in pregnant women	Ceftriaxone 250 mg i.m. + Erythromycin 500 mg 6 hourly x 7 days	Spectinomycin 2.0 g i.m./Ciprofloxacin 500 mg oral single dose/Ampicillin 2 g + probenecid 1 g oral (If penicillin resistance is not of concern) + Erythromycin 500 mg 6 hourly x 7 days
Disseminated gonococcal infection	Ceftriaxone (1 g i.v./i.m. every day)/ Cefotaxime (1 g i.v. every 8 hours) for 7 days; switch to oral cefuroxime (500 mg twice daily) or ciprofloxacin (500 mg twice daily) once severe symptoms resolve	Spectinomycin (2 g i.v. every 12 hours)

(usually in patients with bacteremic illness) and ophthalmia neonatorum (gonococcal conjunctivitis seen exclusively in neonates passing through the infected genital tract of the mother).

Treatment The common regimens used for the treatment of gonorrhea are summarised in Table 8.22. The treatment of partners, investigation of other concomitant STD and counselling are important adjuncts to pharmacotherapy.

Non-gonococcal Urethritis

Etiology The term non-gonococcal urethritis (NGU)[1] refers to infective urethritis not due to gonococcus. C. trachomatis causes about 50 per cent of all cases of NGU and Ureaplasma urealyticum and Trichomonas vaginalis account for the rest.

Clinical features NGU presents as urethritis in men. The clinical differentiation between NGU and gonococcal urethritis is not exact, although there are a few useful pointers (Table 8.22a).

Complications are rare in NGU, though common in gonococcal urethritis. Ascending infection can result in prostatitis, epididymitis and orchitis. Acute urethritis occurs in about 2–3 per cent of cases, principally affecting men below the age of 30 years. Subacute onset of inguinal pain along with swelling of the epididymis occurs and the condition has to be differentiated from torsion of the spermatic cord (which is more abrupt and more painful). Sterility or urethral strictures are uncommon sequelae.

Besides causing urethritis, C. trachomatis infection of the genitourinary tract in women also causes mucopurulent cervicitis. Mucopurulent cervicitis is characterised by a mucopurulent endocervical exudate and local edema.

Diagnosis The diagnosis of NGU is made when N. gonorrhoeae is absent and any of the following three features are found: 1) urethral discharge; 2) 15 or more polymorphonuclear leukocytes (PMNs) per high-power microscopic field in the sediment from the first 10 to 15 ml of voided urine; or 3) an average of four or more PMNs in five high-power fields of a Gram-stain of a urethral exudate or swab specimen. An increased number of PMNs in the urethral exudate is central to this diagnosis. Dysuria in the absence of these diagnostic criteria should not be equated with NGU. *Culture of the urethral discharge for N. gonorrhoeae is required to differentiate definitively between gonococcal and non-gonococcal urethritis*. In over 80 per cent of males with urethritis, a tentative differentiation of NGU from gonococcal urethritis can be made by an examination of

[1] The term postgonococcal urethritis is used for a urethritis syndrome in men that emerges after the treatment of gonorrhea; it is also primarily caused by C. trachomatis.

Table 8.22a Comparison of gonococcal and non-gonococcal urethritis

Clinical feature	*Non-gonococcal urethritis*	*Gonococcal urethritis*
Incubation period	7–21 days	2–7 days
Sexual habits	less sexually active	more active sexually, often a sex worker
Dysuria	variable +/++, symptoms for >4 days	++, symptoms for <4 days
Discharge	scanty, clear (20%), mucopurulent (60%), purulent (20%), non-spontaneous	spontaneous, purulent (80%), mucopurulent (20%), profuse

Gram stain of the discharge for presence or absence of gram-negative intracellular diplococci with the typical appearance of gonococci. Cultures of urethral exudates are required in the remaining 20 per cent for accurate differentiation.

Management Since the culture of C. trachomatis is expensive and serologic tests (ELISA, or direct fluorescent antibody test) are not usually available, an antimicrobial effective against both chlamydial and Ureaplasma organisms is employed in the treatment of NGU or mucopurulent cervicitis. Doxycycline or erythromycin is recommended for the treatment of NGU. Among the quinolones, only ofloxacin (300 mg adminstered orally twice a day for seven days) is an effective regimen for C. trachomatis infection; ofloxacin, however, is expensive and cannot be used during pregnancy or in patients younger than 18 years. Since symptomatic or asymptomatic infection of the sexual partner of an individual with NGU is common, therapy for NGU should be extended simultaneously to the partner to prevent reinfection.

ACUTE PELVIC INFLAMMATORY DISEASE

Acute pelvic inflammatory disease (PID) arises when microorganisms migrate from the vagina and endocervix to infect the endometrium, fallopian tubes, and adjacent structures. Persistent salpingitis leads to infertility, an increased risk of ectopic pregnancy and a high frequency of lower abdominal pain. The major primary pathogens causing PID are N. gonorrheae and C. trachomatis. In addition, facultative and anerobic bacteria (Streptococcus species and Bacteroides species, Escherichia coli, Peptostreptococcus, and Peptococcus) found in fecal and cervicovaginal flora have also been implicated. The role of Mycoplasma hominis and U. urealyticum is less clear.

DISORDERS MANIFESTING AS GENITAL ULCERS

Several of the STD manifest with prominent genital ulceration. Table 8.23 provides a comparative overview of these diseases. Syphilis, chancroid, lymphogranuloma, donovanosis are discussed below. The herpes simplex virus infection is discussed separately under the section on herpes viruses.

Syphilis

Syphilis is a multisystemic sexually transmitted disease caused by the spirochaete *Treponema pallidum.*

Microbiology Treponema pallidum is a spirochaete with a typical corkscrew motility which is seen well on dark field illumination and stains well with silver salts. Humans are the only known hosts for Treponema pallidum.

Epidemiology Syphilis is transmitted almost exclusively by contact with mucocutaneous lesions characteristic of the primary or secondary stage of the disease (see below). An untreated mother can communicate the disease to her fetus (congenital syphilis). A rising incidence of this disease has been seen in recent years, largely related to the rise in AIDS cases (given the propensity of HIV infection to predispose to syphilis).

Pathogenesis Once Treponema enters the body through the skin or mucosal surfaces, it reaches the regional lymph nodes within a few hours. The organism multiplies there and is soon disseminated throughout the body. The host cells mount an inflammatory response characterised by perivascular infiltration with lymphocytes, plasma cells and monocytes. Later on, tissue fibrosis is seen. There is an arteritis of the vessels that leads to swelling of the vascular endothelial cells obliterating the lumen of small arteries in the process (*obliterative endarteritis*). In the late stages of syphilis there is a hypersensitive response to treponemal antigens resulting in granulomatous necrosis (*gumma formation*) in certain tissues (skin and bones).

Table 8.23 Differential diagnosis of genital ulcer syndromes

Feature	*Herpes*	*Syphilis*	*Chancroid*	*Donovanosis*	*Lymphogranuloma venereum*
Organism	Herpes simplex-II	Treponema pallidum	Hemophilus ducreyi	Calymmatobacterium granulomatis	Chlamydiae trachomatis serovar L1–L3
Incubation period	3–7 days	<21 days (up to 90 days)	3–7 days	1–12 weeks	2 weeks
Primary lesion	vesicle	papule	papule or pustule	ulcer	ulcer, noticeable in only 40%
Number of lesions	multiple, may coalesce	usually single	1–3	single or multiple	single
Border	erythematous	sharply demarcated	undermined	serpiginous	erythematous
Depth	superficial	superficial	excavated	superficial	superficial
Base	red and smooth	red and smooth	yellow-grey	beefy red, granulomatous	smooth
Secretion	serous	serous	purulent, hemorrhagic	hemorrhagic	serous
Induration	none	firm	rare	none	none
Pain	+	—	often	±	—
Adenopathy	tender, firm	non-tender, firm	tender, may suppurate	5% have pseudo-buboes	tender
Diagnosis	Tzanck smear	dark ground illumination, other tests	Gram stain	Giemsa stain	serology

Clinical features Fig 8.10 displays the various stages of syphilis. The primary stage is characterised by the appearance of the chancre (hard sore) when the tissue concentration of the spirochaete reaches a critical level. The chancre usually appears in the genital area (the penis in men and the vulva in women) about 3 weeks after the exposure (ranging from 9–90 days), as the tissue concentrations may be highest at the site of inoculation. The ulcer is single, painless, has an indurated base and does not bleed when touched. The regional lymph nodes are enlarged, firm and non-tender (*shotty*). The primary chancre heals spontaneously.

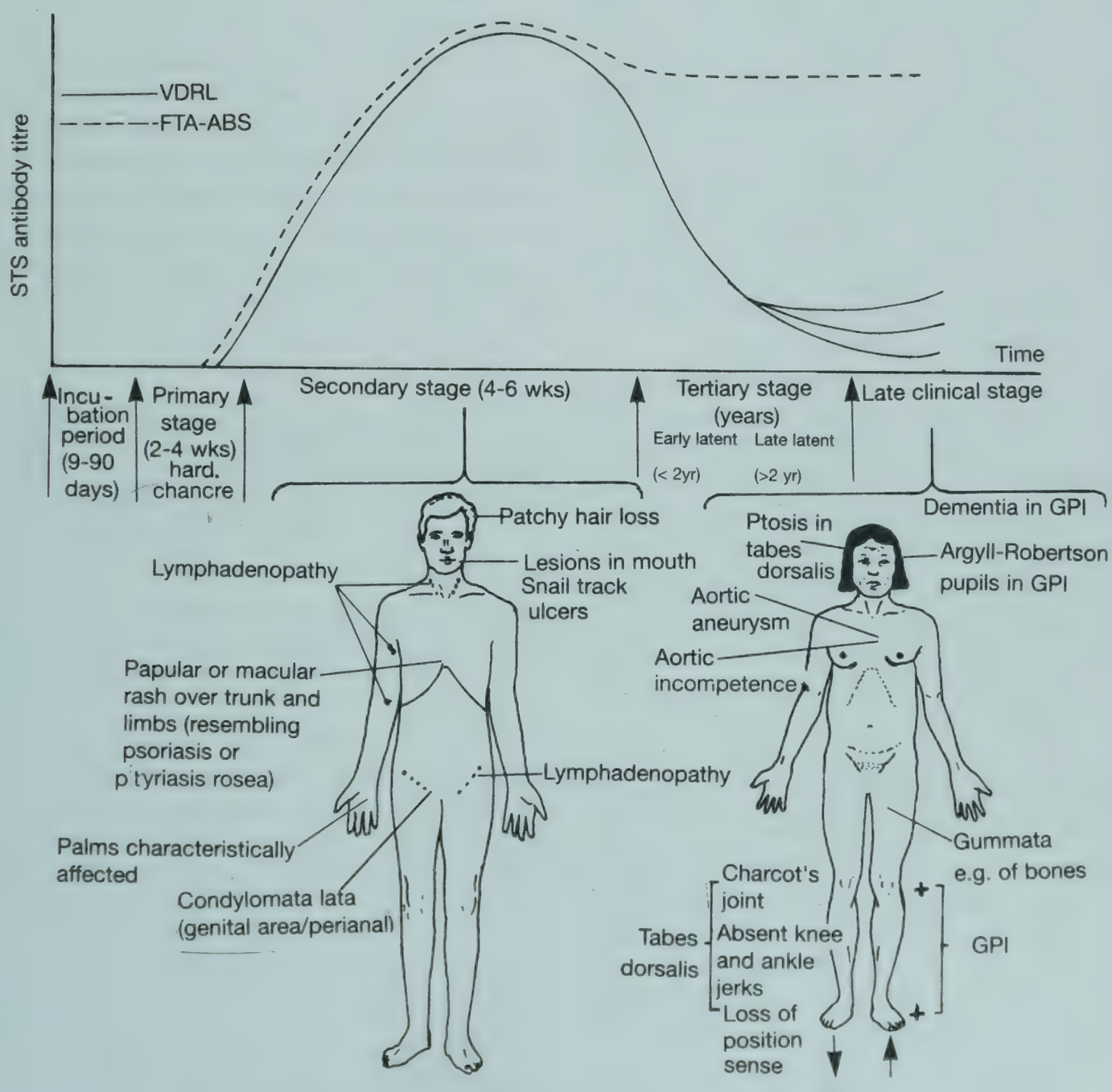


Fig 8.10 Clinical manifestations in relation to serologic tests in syphilis

About 6–12 weeks after the exposure, the secondary stage of syphilis becomes apparent with fever, malaise, headaches and a prominent non-itchy maculopapular rose-coloured rash that typically involves the palms. Vesiculation is not seen in the rash of secondary syphilis. Over 80 per cent of patients have mucocutaneous ulcerative lesions (*snail track ulcers*), principally in the mouth (tongue, palate and pharynx). Such lesions are highly infectious. At the mucocutaneous junctions (especially the anogenital region), there is a hypertrophic skin response and flat, cauliflower-like growths called *condyloma lata* develop. The scalp hair often falls off in a patchy fashion creating a *moth-eaten appearance* (alopecia areata). Generalised lymphadenopathy is an important feature of this stage of the disease. Involvement of the eyes (uveitis), bones (periostitis), kidneys (glomerulitis) or meninges (meningitis) can occur but is usually subclinical. The secondary stage of syphilis lasts about 4–6 weeks.

The patient with untreated secondary syphilis enters the *latent stage* of syphilis. During the early (<2 years) latent stage, mucocutaneous relapses may occur and the patient is infective. Beyond 2 years (late latent syphilis), relapses are rare. Tertiary syphilis develops over several decades in about a third of untreated patients. The lesions of tertiary syphilis are one of three categories: benign tertiary syphilis of the skin, bone and viscera, cardiovascular syphilis and neurosyphilis.

The typical lesion of benign tertiary syphilis is the *gumma*. Cutaneous gummas are nodular ulcerative lesions, whereas gummatous infiltration of the tongue results in chronic interstitial glossitis with leukoplakia. Gummatous osteitis results in deep, boring, nocturnal pain over the involved bones. Cardiovascular syphilis occurs 10–25 years after the initial exposure and the typical lesions are aneurysm of the ascending aorta, coronary osteal narrowing and aortic valvular insufficiency.

Neurosyphilis develops in about 20 per cent of patients with untreated syphilis; of these only a quarter are symptomatic. Asymptomatic neurosyphilis is usually diagnosed on examination of the CSF during evaluation of latent syphilis. It is extremely important to recognise this entity as treatment can prevent progression to symptomatic disease. Three forms of symptomatic neurosyphilis are recognised. *Meningovascular* syphilis is the least common of the symptomatic forms of neurosyphilis. It is the result of diffuse inflammation of the pia-arachnoid along with involvement of the blood vessels. It can present as a stroke, epileptiform attacks (cortical involvement), or as paraparesis (spinal cord involvement) depending on the blood vessel involved. Cranial nerve palsies and pupillary abnormalities occur with basilar meningitis. The *Argyll Robertson pupil* is a small irregular pupil that reacts normally to accommodation but not to light.[1] *General paresis of the insane* (GPI)[2] is the term used to refer to parenchymatous neurosyphilis. The presentation is as a dementia with abnormal pupils, frontal release reflexes, psychotic behaviour and frequent seizures. The third form of symptomatic neurosyphilis is *tabes dorsalis,* a disorder related to demyelination of the dorsal columns, dorsal roots and dorsal root ganglia, characterised by prominent locomotor ataxia. Painful visceral crises and neuropathic joints (*Charcot's joints*) are additional features.

Diagnosis Primary and secondary syphilis can be confirmed by isolating the treponema from the genital ulcer or mucocutaneous lesions using dark field microscopy.[3] Serologic tests are useful for the diagnosis of all stages of syphilis; only the choice of the particular test and the fluid

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[1] Mnemonic: Accomodation Reflex Persists (ARP)

[2] Mnemonic: Personality, Affect, Reflexes (hyperactive), Eye (pupillary abnormalities), Sensorium (hallucinations, delusions), Intellect (dementia), Speech (PARESIS)

[3] In dark field microscopy, light is directed obliquely through the slide so that the rays striking the organisms make them look like bright objects against a dark background.

assessed (blood versus CSF) vary with the stage of the disease and organ involved. In general, two classes of serologic tests are used for the diagnosis of syphilis. The screening tests use non-treponemal lipoidal antigens (cardiolipin) and include the Venereal Disease Research Laboratory (VDRL) test and the Rapid Plasma Reagin (RPR) test. These tests detect what are called reagin antibodies,[1] are non-specific and yield false positive responses in several acute (mycoplasma, infectious mononucleosis, malaria, hepatitis, measles, varicella) and in some chronic diseases (leprosy, autoimmune disease like systemic lupus erythematosus, narcotic addicts). They are, however, inexpensive and easy to perform. These tests usually become positive about 4 to 6 weeks after infection and titres decline with treatment; the antibody may disappear 2 years after the secondary stage.

The second group of tests utilise specific treponemal antigens. The fluorescent treponemal antibody absorption (FTA-ABS) test is the one widely used. These tests are also positive about 3–4 weeks after infection but (unlike the non-treponemal tests) remain elevated for years despite effective treatment.

Treatment Table 8.24 summarises the drug treatment of syphilis based on the stage of the disease. In all but the early infectious cases (<1 year), it is important to carry out a CSF examination to exclude neurosyphilis. Paradoxically, the FTA-ABS test results of the CSF are difficult to interpret; a positive test does not indicate neurosyphilis nor does a negative test exclude the diagnosis. The CSF VDRL test is more helpful; a reactive VDRL test on the CSF is indicative of active neurosyphilis.

[1] Not to be confused with reaginic antibodies which mediate immediate hypersensitivity responses

Table 8.24 Treatment of syphilis according to stage of the disease

Stage	*Primary regimen*	*Alternative*
Early syphilis: primary, secondary, latent <1 year	Benzathine penicillin G (2.4 million units i.m.)	Ceftriaxone 125 mg oral q day × 10 d, OR 250 mg i.m. on alternate days × 5 Doxycycline 100 mg oral twice daily × 14 d Erythromycin 500 mg 6 hourly ×14 d
Latent syphilis: >1 year, cardiovascular syphilis	Benzathine penicillin G 2.4 million units i.m. weekly × 3 doses	Doxycycline 100 mg oral twice daily × 28 d
Neurosyphilis	Penicillin G 12 million units daily × 10 days OR Procaine penicillin G 12 million units/day (along with probenecid 0.5 g 6 hourly) × 10 d	Ceftriaxone 1 g i.v. or i.m. daily × 14 d
Congenital syphilis		
Abnormal CSF	Penicillin G 50,000 units/kg i.v./i.m. × 10 d OR Procaine penicillin G 50,000 units/kg i.m. × 10 d	
Normal CSF	Benzathine penicillin G 50,000 units/kg i.m. single dose	
Syphilis with HIV infection	Penicillin G dose as above but for 14–21 d	Combine penicillin G with ceftriaxone (250 mg i.m. for 10 d)

Chancroid

Chancroid is an acute ulcerative infection of the external genitalia which is caused by the organism *Hemophilus ducreyi* and is transmitted sexually.

Microbiology Hemophilus ducreyi is a small, pleomorphic gram-negative rod that requires special culture media (containing hemin and albumin) for growth.

Epidemiology Chancroid occurs primarily in tropical and subtropical regions. It is one of the most common sexually transmitted diseases encountered in India. Chancroid has been recognised as an important cofactor for HIV transmission (like syphilis and herpes simplex infection).

Clinical features The incubation period of chancroid is 3 to 7 days. The initial lesion appears as a small papule on the external genitalia. Lesions involve the prepuce, coronal sulcus, and frenulum in men, and the labia, clitoris, vestibule, and perianal region in women. The papule rapidly ulcerates (after vesiculation and pustulation). The ulcer is painful, has irregular undermined reddish margins and a purulent base. The ulcer appears soft in consistency (unlike the characteristic 'hard sore' of syphilis), bleeds on touch and is also called a 'soft chancre'. Multiple lesions may be frequently seen. Autoinoculation on the inner aspect of thighs and on the scrotum is common. Roughly half of the infected patients develop unilateral enlargement of the inguinal lymph nodes over the next 7 to 10 days. Inguinal lymph nodes are enlarged, tender, matted together and suppurate resulting in a fluctuant unilocular inguinal abscess (bubo). The bubo may drain spontaneously, discharging its purulent contents and leaving an irregular ulcer crater behind. Mild fever and malaise may accompany the formation of buboes.

Secondary bacterial infection of the genital ulcers by anerobic bacteria (fusospirochaetes) may occasionally ensue, resulting in an erosive, foul-smelling 'phagedenic ulcer'. Complications of chancroid include phimosis and urethral strictures.

Investigations The diagnosis of chancroid is suspected by the presence of multiple, painful exudative genital ulcers, especially if accompanied by tender inguinal adenopathy. Definitive diagnosis requires the isolation of H. ducreyi from the ulcer or inguinal bubo. The culture of H. ducreyi is difficult as the organism is very fastidious and the necessary special media are not freely available in all STD clinics; culture media should contain fresh defibrinated rabbit blood. Dark ground illumination of the ulcer scrapings should be performed and serologic tests for syphilis obtained in order to exclude syphilis. Giemsa stains of scrapings from the ulcer must also be examined for the presence of Donovan bodies, which are diagnostic of granuloma inguinale.

Treatment The recommended treatment for chancroid includes erythromycin (500 mg orally four times a day for seven days), or a single intramuscular injection of ceftriaxone (250 mg). Ciprofloxacin (500 mg orally twice a day for three days) or a combination of amoxicillin and clavulanate (500 mg of amoxicillin and 125 mg of clavulanate orally every eight hours for seven days) are effective alternatives. Resistance to trimethoprim-sulfamethoxazole (80/400 mg, 2 tablets twice daily for 7 days) has rendered this agent a less attractive treatment option. The painful genital ulcer can be treated locally with cold soaks and local application of five per cent aluminum acetate solution. A fluctuant chancroid bubo should be aspirated (to relieve tension) but should not be incised.

Lymphogranuloma Venereum (LGV)

Lymphogranuloma venereum (LGV) is an acute sexually transmitted disease caused by

Chlamydia trachomatis types L1–L3 and is characterised by an evanescent genital lesion followed by inguinal lymphadenopathy.

Epidemiology LGV is a common sexually transmitted pathogen in the tropical and subtropical regions. Sexually active men in the second or third decade of life are commonly affected.

Clinical features Men with LGV present with acute symptoms, whereas women with LGV often present with complications of the disease. A primary genital sore is observed by less than a third of men and rarely by women. In men, the onset of clinical symptoms is often dramatic and is due to the subacute onset of painful inguinal lymphadenopathy about 2–6 weeks after the presumed exposure (the *inguinal syndrome*). Lymphadenopathy is more often unilateral. The involved lymph nodes (also called *buboes*) stretch above and below the course of the inguinal ligament resulting in the so-called *sign of the groove*. The enlarged lymph nodes tend to fuse, soften and break down to form multiple sinuses which discharge thick, yellowish pus; the overlying skin appears like a sieve (*poradenitis*). Sinuses may persist, heal with extensive scarring and fibrosis, and may tend to recur. Occasionally, lymphangitis of the dorsal penile lymphatics may precede the development of buboes; a tender nodular *bubonulus* may be seen along the course of the dorsal penile lymphatics. The bubonulus may rupture into the urethra (forming a fistula) or drain onto the skin (forming a sinus). Occasionally, large polypoid genitoinguinal masses may develop due to lymphatic obstruction (genital elephantiasis). Primary anal or rectal infection is more common in homosexual men.

In women, the genital lymphatic drainage is to the perirectal glands. Proctitis with tenesmus and bloody discharge are the initial symptoms (*anogenitorectal syndrome*). Backache is common. Fever may occur and there may be left lower quadrant tenderness with a palpable pelvic colon on abdominal examination. Later symptoms are due to a cicatricial inflammation of rectal and perirectal tissue. Rectal strictures may develop; symptoms include constipation and passage of 'pencil' stools. Perirectal abscesses, anal and ischiorectal fistulas may be formed. The obstruction of the perianal lymphatics may result in protruding *lymphorrhoids* which grossly resemble hemorrhoids (but contain lymph). Genital elephantiasis (*esthiomene*) may be a complication.

Investigations The typical clinical presentation in men renders the diagnosis easy. Definitive diagnosis requires the demonstration of specific IgM antibodies (microimmunofluorescence test).

Treatment The recommended regimen for treatment of LGV include either doxycycline (100 mg orally, twice daily) or tetracycline (500 mg, 4 times daily) for 14 days. Other effective drugs include erythromycin (500 mg oral, q 6 hours for 2 weeks) or sulfadiazine (1 g oral q 6 hours for 2 weeks). Fluctuant buboes require aspiration through adjacent healthy skin; incision and drainage are contraindicated. Later sequelae such as rectal strictures or fistulas may require surgery. All sexual contacts should be examined and counselled.

Granuloma Inguinale (Donovanosis)

Granuloma inguinale is a slowly progressive chronic ulcerative granulomatous infection involving the external genitalia which is caused by a gram-negative bacterium, *Calymmatobacterium granulomatis.*

Microbiology *Calymmatobacterium granulomatis* is an encapsulated gram-negative bacterium which appears in Giemsa-stained tissue scrapings as a dark-staining rod-shaped

inclusion within the cytoplasm of tissue macrophages (the *Donovan body*).

Epidemiology The disease is acquired through sexual contact with an infected partner. Concomitant infection by other sexually transmitted pathogens is common.

Clinical features The incubation period ranges from 2–12 weeks. The initial lesion appears as a painless papule on the penis, scrotum, groin, vulva, vagina or rectum. About half of the lesions occur on the genitals, the remaining are found in the perianal, perineal or the inguinal region. The papule ulcerates, resulting in a beefy-red granulomatous mass with rolled, raised, margins. The lesion bleeds easily when scraped. Contiguous lesions tend to coalesce and extend subcutaneously into the surrounding inguinal tissues; this can result in inguinal pseudobuboes, which may be confused with inguinal adenopathy. Healing is slow and tends to be cicatricial and can result eventually in genital lymphedema. Secondary bacterial infection of the genital ulcers may occur. Rare complications include the destruction of external genitalia, and fistula formation. An association with squamous cell carcinoma of the skin has been reported.

Investigations The diagnosis is suspected when there are typical beefy-red granulomatous genital lesions and is established by the demonstration of Donovan bodies within tissue macrophages in Giemsa-stained crush preparations of tissue from the edge of the lesion. A coincidental syphilitic chancre must be excluded by dark field examination and appropriate serologic tests for syphilis.

Treatment Tetracycline (500 mg orally, four times a day) administered for 3 weeks is the treatment of choice. Therapy is usually continued until Donovan bodies are no longer seen in tissue smears and until the skin lesions heal. Alternative antibiotic regimens have included streptomycin (1 g i.m., daily for 2 weeks), trimethoprim-sulfamethoxazole (80/400 mg, 2 tablets twice daily for 2 weeks), and doxycycline (100 mg twice daily for 2 weeks). Surgery may be required to resect pseudobuboes and to correct other cicatricial complications of granuloma inguinale.

DISEASES CAUSING GROWTHS IN THE GENITAL REGION

Genital Warts

Genital warts are caused by viruses belonging to the genus papilloma virus, a member of the family papova viruses. Genital warts are also called *condylomata acuminata.* Papilloma virus types 6 and 11 are primarily associated with genital warts. If genital warts are due to papilloma viruses 16, 18 or 31, there is a high incidence of malignant transformation.

Clinical features After an incubation period of 1 to 10 months, the genital lesion appears as small tumour-like excrescences which eventually grow into cauliflower-like masses. The lesions are typically soft, filiform and are seen on the glans penis, vulva, vagina and the perianal region. They usually do not cause symptoms other than those due to their morphologic appearance.

Treatment Several treatment options are available. Laser treatment is effective but is also associated with a high relapse rate. Cryotherapy is an option, if available at the treatment centre. Topical podophyllin (crude extract of the plant Podophyllum peltatum) is used for extragenital and vulvar warts. The drug is applied at weekly intervals and washed off after about 6 hours. Podofilox is a newer less toxic (but more expensive) derivative which can be applied twice daily for 3 days followed by a rest period of 4 days. The cycle may have to be repeated 4 times. Intralesional injections of α-interferon (2–3 times a week) are also reported to be highly effective.

KEY CONCEPTS

Sexually Transmitted Diseases

Gonorrhea

- STD due to gram-diplococcus (*Neisseria gonorrhoeae*) in sexually promiscuous young adults.
- Causes purulent urethritis in men, cervicitis in women, oral and anal lesions in both (orogenital sex), ophthalmia neonatorum in infants born through infected birth passages.
- Spectrum of invasive disease: PID, tuboovarian mass, salpingitis with increased risk of ectopic gestation; perihepatitis; arthritis-dermatitis syndrome.
- Diagnosis by Gram-stain of urethral exudate; blood cultures positive in 25% with disseminated infection. Exclude other concomitant STD.
- Treat uncomplicated infections with single dose ceftriaxone + doxycycline (7 days); for complicated infection: cefoxitin i.v./ceftriaxone i.m + doxycycline (14 days).

Non-gonococcal Urethritis

- Etiology includes Chlamydia trachomatis and Mycoplasma urealyticum.
- Subacute urethritis with mucopurulent discharge in men; women often have asymptomatic cervicitis. Complications in women: salpingitis, PID, bartholinitis.
- Diagnosis by examination of exudate which is for gonococci.
- Treat with erythromycin or doxycycline.

Syphilis

- Multiphasic disease due to corkscrew spirochaete *Treponema pallidum.*
- *Primary* syphilis is characterised by primary chancre: painless genital ulcer which is associated with shotty inguinal lymph nodes; heals in 3–6 weeks. *Secondary* syphilis: mucous ulcers, condylomata lata at mucocutaneous junctions, rash involving palms and soles, uveitis. *Latent* syphilis is an asymptomatic period after secondary syphilis. *Tertiary* syphilis is of several types. *Benign gummatous* syphilis typically occurs 3–10 years later and involves bone and mucocutaneous regions. *Cardiovascular* syphilis: occurs 10–25 years later; ascending aortic aneurysm, aortic regurgitation due to root dilatation, coronary ostial stenosis. *Neurosyphilis* may be meningovascular (strokes), parenchymatous (tabes, GPI) or gummatous.
- Diagnosis of primary stage is by demonstrating organism in exudate with dark ground illumination; later diagnosis by serology: VDRL, FTA-Abs.
- Treatment consists of intramuscular benzathine penicillin; aqueous penicillin (21 days) used for neurosyphilis and cardiovascular syphilis.

Chancroid

- STD due to *Hemophilus ducreyi* which is common in developing countries, and is associated with HIV infection.
- Mostly men are affected. Manifests as a painful genital ulcer, which is associated with painful inguinal lymphadenopathy. Severe tissue destruction may ensue.
- Diagnosis is often based on clinical findings (and negative bacteriology for other STD) because it is difficult to demonstrate the organism.
- Treatment: erythromycin (7 days) or single dose ceftriaxone i.m.

Lymphogranuloma venereum

- STD due to Chlamydia trachomatis serovars L_1–L_3.
- Primary lesion may be transitory and is followed by suppurative inguinal lymphadenitis (*buboes*) that discharge with multiple fistulae and sinuses. Women have urethritis, endometritis and suppuration of perirectal lymph glands. Genital elephantiasis is a sequel.
- Diagnosis is by specific complement fixation test.
- Treatment: doxycycline/erythromycin/tetracycline for 14 days.

Granuloma inguinale

- Caused by *Calymmatobacterium granulomatis.*
- Chronic granulomatous lesion which begins as a beefy-red genital nodule. It heals with cicatrisation.
- Diagnosis is by demonstrating *Donovan bodies* within macrophages on examination of scrapings obtained from the ulcer.
- Treatment: Streptomycin/tetracycline/erythromycin (21 days).

Genital warts

- Genital excrescences (condylomata acuminata) caused by human papilloma virus. Warts occur on the penis/vulva and have a soft, pink, cauliflower appearance.
- These warts must be differentiated from condyloma lata and malignancy; this may require biopsy.
- Treat with topical podophyllin or laser ablation.

8.7 Viral diseases

MYXO- AND PARAMYXOVIRUSES

Influenza

Microbiology Three genera of influenza viruses (A, B, C) have been identified; of these, Influenza A and B viruses are important causes of human disease. Influenza viruses are enveloped single-stranded RNA viruses; the envelope is covered with spike-like surface projections composed of antigenic glycoproteins which have either hemagglutinin or neuraminidase activity. Hemagglutinins help in viral binding to the receptors on respiratory epithelial cells, whereas the neuraminidase aids in virion release from infected cells by attacking sialic acid present on host cell surfaces. Influenza A virus carries one of three hemagglutinins (H1, H2, or H3) and either of two neuraminidases (N1 or N2). By changing the antigenic composition of the envelope, influenza viruses dodge host immune responses.

Epidemiology Five worldwide pandemics of influenza have been reported over the past 100 years. Infection is most common in winter. All segments of the population are susceptible, although complications of infection are more frequent in the very young and the elderly; individuals with cardiopulmonary disease are particularly vulnerable. Infection is transmitted through person to person contact by way of airborne droplets. The incubation period is 1–3 days. The severity of a given influenza outbreak depends on the status of immunity in the community.

Pathogenesis Viral replication within the respiratory epithelial cells results in diffuse mucosal inflammation with hyperemia and edema. Mucosal regeneration after denudation may take three to four weeks. Impaired mucociliary clearance mechanisms and the denuded epithelial surface predispose to secondary bacterial superinfection.

Clinical features Influenza begins with the abrupt onset of severe systemic symptoms, which typically include fever, headache, diffuse myalgia, and marked prostration. A non-productive cough caused by nasopharyngitis or lower respiratory tract involvement is frequent. The acute illness subsides spontaneously within three to five days, but the cough can persist longer.

The complications of influenza may result from the involvement of the lower respiratory tract either by the progression of the viral process itself or as a result of secondary bacterial infections. Primary viral pneumonia occurs in the first week of illness and manifests as high fever with a severe non-productive cough; a progressive dyspnea develops in most patients. Physical examination reveals tachypnea, and respiratory distress; pulmonary findings may be scanty in contrast to the clinical symptoms. A secondary bacterial pneumonia (usually due to Streptococcus pneumoniae, Staphylococcus aureus or Hemophilus influenzae) may complicate influenza. It occurs typically after an afebrile interval, is more common in patients

vith chronic bronchitis, and portends a more erious prognosis than primary viral penumonia. Extrapulmonary complications of influenza nclude myopericarditis, myositis, transverse nyelitis, encephalitis, and the Landry-Guillain-Barre syndrome. The Reye syndrome has been eported in children given aspirin during an pisode of influenza.

Diagnosis The clinical picture of a viral upper espiratory illness with severe systemic ymptoms and marked prostration is usually nough to make a clinical diagnosis of influenza. The Gram-stain of the sputum or its culture fail o reveal bacterial pathogens. In cases with viral neumonia, the chest X-ray reveals diffuse nterstitial infiltrates, and arterial blood gas eterminations confirm hypoxemia.

A definitive diagnosis requires isolation of the irus from nasopharyngeal washings or emonstration of a fourfold rise in antibody tres in paired sera.

Management The treatment of influenza is nainly supportive, with bed rest, ensuring roper hydration and administering antipyretics or lowering fever. It is important to identify atients who develop viral pneumonitis and equire intensive monitoring. It is also important o be vigilant for complications as a result of econdary bacterial pneumonia.

Prevention Yearly vaccination of susceptible ndividuals with a vaccine containing antigens rom the strains expected to predominate that eason has markedly reduced morbidity ssociated with influenza. Furthermore, two ntiviral drugs, amantadine or rimantadine, can meliorate symptoms if administered within 8 hours of they onset of symptoms.

Parainfluenza

Microbiology Parainfluenza is caused by a aramyxovirus, an enveloped single-stranded NA virus. Unlike the influenza viruses, the parainfluenza virus has an envelope which hemagglutinin and neuraminidase proteins that are antigenically stable. Four serotypes of pathogenic parainfluenza virus have been recognised, of which type 3 is most likely to be associated with serious disease.

Clinical features Parainfluenza viruses are spread from person to person by direct contact or by aerosols. Infants and young children between five months and five years of age are commonly affected. The spectrum of the disease ranges from mild nasopharyngitis to croup, bronchitis, and even pneumonia.

Treatment The treatment is symptomatic.

Respiratory Syncytial Virus

Microbiology Respiratory syncytial virus (RSV) is a major pathogen of infants and young children. Although RSV is also a paramyxovirus, its envelope lacks both hemagglutinin and neuraminidase antigens. The viral envelope does have two other unique glycoproteins which appear to play a pathogenetic role: 1) the G protein, which mediates RSV attachment to human respiratory epithelial cells; and 2) the F protein, which initiates fusion the of viral and host cell membranes.[1]

Clinical features RSV is a major cause of community-wide outbreaks of acute respiratory tract infections. Most cases are self-limited and mild. Symptomatic disease usually affects infants and very young children, and symptoms appear to be most severe in those who are less than five months of age. The virus causes nasopharyngitis, conjunctivitis, and otitis. It can spread to the lower respiratory tract and cause a viral bronchiolitis or a viral pneumonia. In healthy adults, RSV causes either a subclinical infection or a mild upper respiratory tract infection.

[1] The F protein also promotes membrane fusion between the infected and non-infected host cells, thus creating the cellular syncytium from which the virus gets its name.

However, RSV infections can be virulent in immunocompromised patients, and in the elderly.

Diagnosis and treatment RSV infection can be diagnosed by viral isolation or by serology. The majority of infections are self-limited. Chemotherapy with ribavirin may be required for hospitalised infants with severe lower respiratory tract involvement.

MUMPS

The virus is a pleomorphic, enveloped, single-stranded RNA paramyxovirus. Humans are the only natural hosts of the mumps virus.

Epidemiology Mumps is endemic worldwide. In urban populations, the seroprevalence exceeds 90 per cent in persons above 15 years. Infection is rare in infants because of the protective effect of maternal antibodies. The incidence of mumps has dropped dramatically after the introduction of vaccination. Mumps is most common in the age group 5 to 15 years. Infection is more common in winter and spring. Mumps is spread from person to person through direct contact with oropharyngeal secretions from an infected individual. The incubation period ranges from 12 to 25 days (mean 18 days). The virus is shed in saliva anywhere from six days before, to nine days after the onset of parotid swelling.

Pathogenesis The virus multiplies in the pharynx, and this is followed by viremia, with potential spread to many organs. Parotitis results from the infection of ductal epithelium following viremic spread to the gland.

Clinical features About a third of mumps cases are asymptomatic. In symptomatic cases, there is an initial prodromal phase with fever and malaise predominating. Swelling of the parotid gland and pain are characteristic features. Parotid swelling commences behind the jaw and the neck and then spreads forward. Papillitis may be visible at the orifice of the Stensen's duct in the mouth. Parotid involvement may be unilateral, and other salivary glands may be involved. The glands attain their maximum size in 3 to 4 days and then the swelling subsides in about a week. Epididymo-orchitis occurs in approximately 20 per cent of postpubertal males with mumps and is usually unilateral. Although some testicular atrophy generally occurs, sterility is uncommon. Asymptomatic involvement of the central nervous system is common. At least 50 per cent of patients with mumps have demonstrable cerebrospinal fluid pleocytosis. Symptomatic meningitis is less common and usually presents as an aseptic meningitis. Symptomatic encephalitis is an infrequent complication (1 in 6,000) which manifests as altered sensorium, with or without focal neurologic deficits. Other rare complications of mumps are pancreatitis, mastitis and oophoritis. Mumps is a rare cause of arthritis; it generally affects young males, can be mono- or polyarticular, and is usually self-limited.

Diagnosis The diagnosis of mumps is easy in an unvaccinated child with tender unilateral or bilateral parotitis. The other causes of parotid swelling which must be considered in the differential diagnosis in older individuals include bacterial parotitis, granulomatous infiltration (for example sarcoidosis), parotid tumours and chronic alcohol abuse.

Routine laboratory data are usually of no assistance in the diagnosis of mumps. The white blood cell count is usually normal or low although leukocytosis may accompany orchitis, pancreatitis, or encephalitis. The CSF profile is characterised by mild lymphocytic pleocytosis, an elevated protein level, and normal (90%) or low (10%) glucose level; a lumbar puncture is not indicated in the absence of symptomatic neurologic disease. A definitive diagnosis of mumps can be established by the demonstration

of a serologic rise in specific antibody, or by virus isolation though this is usually not necessary.

Management Therapy for mumps is mainly supportive. Anti-inflammatory agents may have a role in treating mumps orchitis.

Prevention The cornerstone of prevention of mumps is vaccination; live, attenuated mumps vaccine derived from the Jeryl Lynn strain is safe and induces seroconversion in more than 90 per cent of recipients. It is available both as a monovalent vaccine and as a component of the MMR vaccine, which is the preparation used most commonly. It is currently recommended that children be vaccinated with the MMR preparation at the age of 15 months.

HERPES VIRUSES

Human herpes viruses are a group of seven double-stranded DNA viruses: herpes simplex virus types 1 and 2, varicella-zoster, cytomegalovirus, Epstein-Barr virus, and human herpes virus types 6 (HHV-6) and 7 (HHV-7).

Herpes Simplex Virus Infections

This group consists of two viruses, Herpes simplex types 1 and 2 (HSV-1 and HSV-2). The two types share considerable similarity in their genetic make-up. Clinical illness patterns differ for the two viruses. 75 per cent of HSV-1 infections are above the waist whereas 75 per cent of HSV-2 infections are below the waist. HSV-1 is spread by close contact. HSV-2 is a sexually transmitted disease.

Pathogenesis and clinical features The portals of entry for HSV are the oral or genital mucosa. Viral transmission seems increased during symptomatic infections, primary infections and from men to women. After inoculation, herpes viruses spread from the mucous membrane or abraded skin along nerve pathways to the dorsal root or cranial nerve ganglia. The virus replicates within the ganglia and returns by the same path and causes the typical vesicular skin lesions. The neurons themselves do not seem to be affected.[1] The nerve ganglion serves as a reservoir for the dormant virus which periodically becomes activated and proceeds to the mucocutaneous/cutaneous surfaces to cause recurrent painful vesicles. Immunity is mediated by the cellular immune response; patients with defects of cell-mediated immunity are susceptible to recurrent, prolonged and more severe attacks.

The hallmark of HSV infection is the appearance of crops of painful grouped vesicles that have an erythematous base. Fever and tender lymphadenitis may be associated. The vesicles heal with ulceration. The vesicles can be located anywhere in the body but typically occur in the perioral region (*febrile blister* or *cold sore*), mouth (*herpetic stomatitis*), perianal region, conjunctiva (*herpetic keratoconjunctivitis*) periungual region (*herpetic whitlow*), or scattered over the trunk (usually among wrestlers as a result of close contact; also called *herpetic gladiatorum*).

The most devastating complication is herpes simplex *encephalitis* (HSE). HSE is discussed in detail in the section 'Infections of the Nervous System'.

Recurrences of herpes are usually milder, less painful and last half as long as the primary episode.

Diagnosis The differential diagnosis of genital ulcers has been discussed in a previous section. A *Tzanck smear* of the vesicle is diagnostic[2] but does not permit distinction from the varicella zoster virus.

Treatment Symptomatic treatment consists of cool compresses and local anesthetics for

[1] This is generally true but herpes simplex has now been identified as the causative agent of Bell's palsy.

[2] The roof of the intact vesicle is ruptured gently and the base scraped. The material is placed on a slide, air-dried and stained with Giemsa or Wright's stain. Appearance of multinucleated giant cells is pathognomonic.

soothing the painful lesions. Specific treatment consists of acyclovir. Acyclovir has revolutionised the treatment of HSV infections. Primary infections are treated with a dose of 200 mg, 5 times a day for 10 days. Treatment of recurrences is less justifiable; oral recurrences should not be treated with acyclovir and a shorter course of 5 days of acyclovir may be used for disabling genital recurrences (200 mg, 5 times a day begun within 24 hours of symptoms). Prophylactic acyclovir has been used (400 mg bd or 200 mg tid) to prevent recurrences but stoppage of medication is associated with prompt recrudescence.

Varicella Zoster Virus Infections

The varicella zoster virus causes chicken pox (a predominantly pediatric disease) and herpes zoster (a disease of adults). Only herpes zoster is discussed here as detailed discussions of chicken pox are provided by pediatric texts.

Herpes Zoster

Herpes zoster is a viral disease which results from reactivation of the varicella zoster virus which has been dormant in the dorsal root ganglia after the primary infection, and is characterised by a vesicular skin eruption.

Epidemiology Herpes zoster occurs in about 20 per cent of the population sometime during their life. Men and women are equally affected. Incidence increases with age and is more common in immunocompromised subjects. Patients with zoster can cause chicken pox in the non-immune contacts.

Pathology The involved dorsal root ganglion is swollen, shows marked hyperemia, lymphocytic infiltration with areas of necrosis, and minute hemorrhages.

Clinical features Herpes zoster is a biphasic illness. The prodromal phase is characterised by sensory changes in the involved dermatomes; burning, tingling or itching sensations are common. Hours to days later, the acute phase is heralded by the appearance of a rash. The rash of zoster is typically erythematous and maculopapular initially, and rapidly evolves into grouped vesicles. The diagnostic feature of herpes zoster is the dermatomal distribution (area supplied by a dorsal root) of the rash. Thoracic dermatomes are more frequently involved. If three or more different dermatomes are involved, an underlying immunodeficient state is strongly suggested.[1] Constitutional symptoms are prominent at this stage of the illness; low-grade fever, malaise and headache are common. The vesicles soon collapse and dry with crust formation over the next 7–10 days. Residual hyperpigmentation may be seen.

Herpes zoster ophthalmicus affects the ophthalmic branch of the trigeminal nerve. Corneal vesicles may ulcerate and heal with scarring, with consequent impairment of vision. Concomitant involvement of the third cranial nerve may result in ptosis and squint. Herpes of the geniculate ganglion (*Ramsay-Hunt syndrome*) is characterised by painful vesicles in the external auditory meatus (behind the ear, in the canal and on the tympanic membrane) and on the fauces. A facial paresis is seen, with loss of taste over the anterior two-thirds of the tongue. Auditory or vestibular symptoms (hyperacusis, vertigo, hearing loss) may be seen.

An additional (third) component of the illness is encountered in about 15 per cent of patients who develop a chronic pain syndrome, termed postherpetic neuralgia, after the rash has healed. This complication is more common in the elderly and typically lasts for about a month or two. Two types of pain are described: paroxysmal and lancinating or steady and burning. Pain is often aggravated by light touch on the skin in the area of the initial eruption. Other rare complications of zoster include a meningoencephalitis, transverse myelitis, cutaneous dissemination and involvement of other visceral organs (pneumonitis, hepatitis, myopericarditis cystitis).

[1] Such disseminated zoster is an 'AIDS-defining condition'

Diagnosis The diagnosis of herpes zoster is usually clear from the typical dermatomal vesicular rash. If confirmation of diagnosis is deemed essential, a Tzanck smear shows typical multinucleate giant cells.[1]

Treatment Acyclovir is highly effective against zoster but the dose required is four times that used to treat herpes simplex infections. If begun within 48 hours of the appearance of the rash, the time to crusting (of the rash) as well as the severity and frequency of post-herpetic neuralgia are reduced. An oral dose of 800 mg 5 times a day for 7 days is used in uncomplicated zoster. If dissemination is present, the patient must be hospitalised for intravenous administration of acyclovir (10 mg/kg every 8 hours for 10 days). Analgesics are indicated for the acute pain of zoster. Treatment of post-herpetic neuralgia is challenging and remains empirical. Topical agents like Capsaicin ointment,[2] or systemic therapy with anti-depressants (tricyclics, fluoxetine, trazodone), anticonvulsant agents (carbamazepine), phenothiazines and H2-receptor antagonists (cimetidine) have all been tried with variable degrees of success.

Cytomegalovirus (CMV)

CMV is a ubiquitous herpes virus that causes a form of mononucleosis in immunocompetent adults and a disseminated disease in the immunocompromised host and the fetus.

Epidemiology CMV is transmitted by close contact with infected individuals. CMV is present in blood leucocytes, and other body secretions (semen, saliva, maternal milk, and urine). Adults are most often infected through the genital route. The virus can spread to the fetus by the transplacental route. Blood transfusions and organ transplantation are other uncommon sources of transmission of CMV.

Clinical features

Young adults: CMV mononucleosis, a self-limiting disease lasting 2–4 weeks is the usual manifestation in immunocompetent adults. Generalised lymphadenopathy is associated with fever, malaise, myalgia and splenomegaly.

Immunosuppressed individuals: Disseminated disease involving the lungs, gastrointestinal tract, central nervous system, or eyes, develops in these individuals. CMV retinitis is important to recognise as it is a treatable cause of blindness. Early lesions consist of small white areas of retinal necrosis; later lesions consist of areas of retinal hemorrhage, vessel sheathing, and edema.

Fetus: Fetal infection is characterised by disseminated disease. Most congenital infections are asymptomatic. Occasionally, a florid presentation is seen in the neonate with jaundice, petechiae, microcephaly, intracerebral calcification, hepatosplenomegaly, interstitial pneumonitis, and retinitis.

Diagnosis Routine biochemical tests may show abnormalities of liver function (moderate elevation of transaminases) and the peripheral blood may show lymphocytosis (with >10% atypical lymphocytes). Definitive diagnosis requires viral isolation (from secretions or infected tissues) or a positive serology.

Treatment Ganciclovir (5 mg/kg i.v. twice daily or as an ocular implant) and foscarnet are effective in the treatment of CMV retinitis in HIV-infected patients. The drugs can be used separately, although recently combined regimens have shown promise.

Epstein-Barr Virus Infections

Epidemiology The epidemiology of Epstein-Barr virus infection in developing countries differs from that in developed countries. In developing countries infection occurs early in life, is usually inapparent and immunity is acquired resulting in seropositivity by the age of

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[1] Present in herpes simplex infection also

[2] An agent that inhibits the release of substance P

6 years. In developed countries, where a significant proportion of the population is non-immune, a mononucleosis syndrome develops in adolescent boys and girls. Saliva is the vehicle of spread of infection, both in childhood and in adolescence. In the latter age group, kissing has been documented to result in transmission of the virus.

Pathogenesis and clinical features The virus proliferates at the portal of entry—the nasopharynx. Thereafter, it replicates within the B lymphocytes. B lymphocytes serve to disseminate the virus throughout the lymphoreticular system. In fact, the Epstein-Barr virus persists lifelong within some of the B lymphocytes. After an incubation period of 4–7 weeks, the typical picture of *infectious mononucleosis* appears in non-immune teenagers and young adults. This is characterised by the insidious onset of low-grade fever, malaise, which soon gives way to the typical picture of tonsillitis, pharyngitis, tender lymphadenitis and moderate-grade fever. The symmetric involvement of the posterior cervical lymph nodes is typical. Pharyngitis is often exudative and palatal petechiae may be seen. In some individuals lymphadenopathy is more prominent than pharyngitis and still others have a mainly febrile episode (typhoidal form of illness) with scanty findings on examination. A maculopapular rash may be seen, especially in individuals treated with ampicillin (due to a mistaken diagnosis of bacterial sore throat). Anorexia and nausea are common during the illness, presumably reflecting a mild hepatitis. Jaundice or palpable hepatomegaly are rare. Splenomegaly is more frequent, being present in upto 50 per cent of patients. The illness runs a self-limited course of 1–2 weeks.

Complications of Epstein-Barr infection are rare. They include hepatitis, and a variety of neurologic (Guillain-Barre syndrome, facial nerve palsy, meningoencephalitis, transverse myelitis) and hematologic (thrombocytopenia, disseminated intravascular coagulation) syndromes. Obstruction of the upper airway due to massive lymphoid hyperplasia has been reported. Splenic rupture is a very rare complication.

Diagnosis Findings in the peripheral blood are distinctive in infectious mononucleosis. There is a leucocytosis (generally in the range 10,000–20,000/mm^3) with more than 50 per cent lymphocytes. Also present in the peripheral blood are atypical lymphocytes,[1] called *Downey cells*; these cells are large, have a vacuolated basophilic cytoplasm with rolled up edges and look like large lymphoblasts. The biochemical tests may reveal mild derangement in the liver function tests.

The classic serologic finding in infectious mononucleosis is the presence of heterophil antibodies.[2] These antibodies are detected by the 'mononucleosis rapid slide agglutination test' (also called the *Monospot test*). Heterophil antibodies are positive in 75 per cent of patients at the beginning of the second week and in 80–90 per cent of patients by the third week of illness. However, heterophil antibodies are not specific for the Epstein-Barr virus; they are seen in lymphoproliferative disorders, toxoplasmosis, cytomegalovirus infection, rubella and HIV infections. Specific antibodies against Epstein-Barr virus include antibodies directed against the virus capsid antigen (VCA), early antigen (EA) and Epstein-Barr nuclear antigen (EBNA); these antibody tests are not available in all laboratories. When available, tests for these antibodies are more definitive for the Epstein-Barr virus. IgM and IgG antibodies against VCA are positive during the acute phase and anti-EBNA IgG antibodies appear during convalescence.

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1 These cells are also found in several viral infections but are >10% of all lymphocytes only in Epstein-Barr virus infection, cytomegalovirus infection and toxoplasmosis.

2 They are so called as they are directed against phylogenetically unrelated antigens, e.g. antibodies against sheep red blood cells.

Treatment Treatment of Epstein-Barr virus infection is mainly symptomatic. Non-steroidal antiinflammatory drugs or acetaminophen help relieve throat discomfort and fever. The use of steroids has been controversial and they should only be used for severe airway obstruction, or if severe hemolytic anemia or thrombocytopenia are present.

RETROVIRUSES

Retroviruses are a group of single-stranded RNA viruses which have the enzyme *reverse transcriptase* which enables them to synthesise DNA using viral RNA and the host cell machinery. Human retroviral infections are due to a group called *human T cell lymphocytotropic viruses (HTLV)*. Most people infected with HTLV-I are asymptomatic; a minority develop adult T cell leukemia-lymphoma or tropical spastic paraplegia (HTLV-associated myelopathy). HTLV-II has not been associated with any illness, other than some reports of isolation of the virus from patients with hairy cell leukemia. HTLV-III is also called the human immunodeficiency virus (HIV). Two types are described, that is, HIV-1 and HIV-2, of which the former is more common.

Acquired Immunodeficiency Syndrome (AIDS)

Acquired Immunodeficiency Syndrome (AIDS) is a chronic disease due to infection with the retrovirus human immunodeficiency virus (*HIV-1*). It is characterised by a wide clinical spectrum that ranges from an asymptomatic phase, to symptoms suggesting mild to moderate immunologic dysfunction, to complications indicating profound immunosuppression.

Etiology HIV-1 is a retrovirus belonging to the *lentivirus* family. Lentiviruses generally cause chronic indolent infections with a long latency period, persistent viremia and nervous system involvement. HIV-1 is composed of a central cylindrical core of diploid RNA consisting of three genes: *pol, gag,* and *env* that are located between long terminal repeat segments (*ltr*). Pol codes for *reverse transcriptase* and endonuclease, gag codes for p24, a structural protein found in the core, and for other core proteins (p17, p9, p7). Env codes for two glycoproteins, gp 41 (a transmembrane protein) and gp 120 (which protrudes from the envelope), which are part of the viral envelope and are important for HIV to attach to its target lymphocyte cell.

Pathophysiology HIV virus targets a subset of T lymphocytes known as helper/inducer or CD_4^+ cells, monocytes, macrophages and their hematologic precursors. The clinical consequences of HIV infection are mainly the result of depletion of CD_4^+ cells. The HIV gp 41 envelope protein binds to CD4 receptors and the virus fuses with the cell membrane. Once within the cytoplasm of the host cell, reverse transcription occurs: DNA is made from the viral RNA template. Infected cells remain dormant for a variable period of time. When activation occurs, proviral DNA transcribes genomic and messenger RNA and new virions are synthesised. New virions may bud from infected cells and circulate to infect new target cells; infected cells may also fuse directly with uninfected CD_4 cells, thereby avoiding exposure to neutralising antibodies. Monocytes and macrophages serve an important role in the pathogenesis of HIV infection; these cells survive viral replication and carry the virus to various body sites. Infection of the central nervous system occurs by infected macrophages which carry the HIV across the blood-brain barrier.[1]

Neurologic damage occurs by cytokines released from macrophages (innocent bystander), by viral interference with calcium channel function or its competition with the neurotrophic function of vasoactive intestinal peptide.

[1] Also called the *Trojan horse* mechanism

HIV infection results in decreases in CD_4 cells and a relative increase in CD_8 (suppressor/cytotoxic) T lymphocytes. In end-stage HIV infection both CD_4 and CD_8 cells lines are depleted. Functional impairment of CD_4 cells progresses as HIV disease progresses. A polyclonal hyperglobulinemia is seen but B lymphocyte response to antigens is impaired.

Epidemiology Although the majority of AIDS cases have occurred in developed countries, an HIV epidemic is presently raging through the developing countries as well. The WHO reports that over 2.5 million cases of AIDS have occurred worldwide, with upto 14 million people known to have HIV infection. An estimated 2 million people are believed to be infected with HIV in India and Southeast Asia alone. The HIV epidemic was initially established in India along the east and west coast. Infection was highest in the urban areas but the rural population is being increasingly infected as well (Fig 8.11). The commercial sex environment and genital ulcer disease are major contributing factors in India. In India and developing countries, there is a dominance of heterosexual sex as the major mechanism of HIV transmission; this explains the similar distribution of cases in men and women and the high rate of pediatric HIV infection. Truck drivers who drive across the country are an important source of HIV dissemination. Paid blood donors as well as improper or inadequate screening for HIV in blood banks are key contributory factors. In the northeast state of Manipur in India, there is a high prevalence of intravenous drug abuse and this contributes to HIV disease in this area.

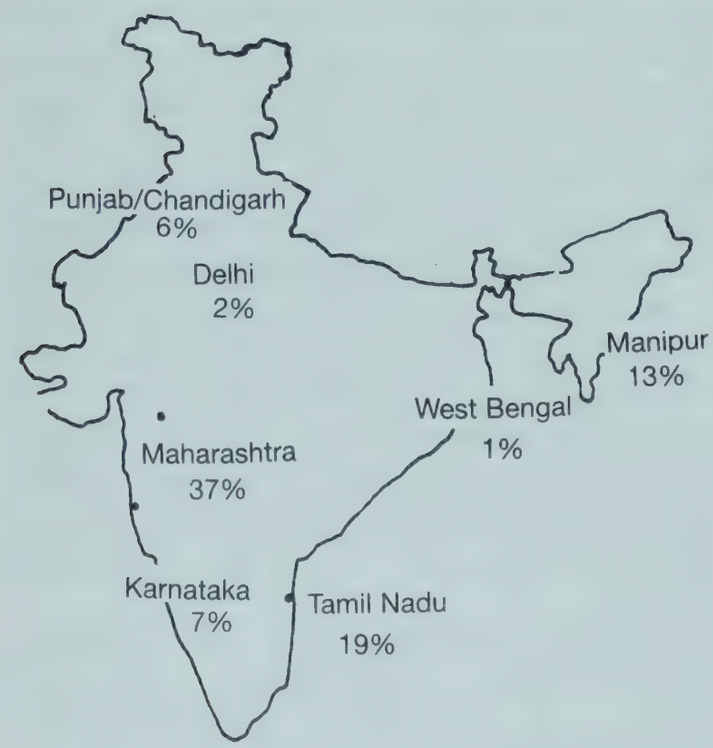


Fig 8.11 The percentage of 14,807 HIV infections from various Indian States/Provinces reported to the National AIDS Control Organization of India, February 1994

The clinical features of AIDS are discussed in detail below. Only important epidemiological differences in manifestations are pointed out here. The pattern of disease in India is similar to that in other developing countries with tuberculosis being the dominant opportunistic infection (Pneumocystis being uncommon). Early cases of AIDS reported from south India were in individuals with non-Hodgkin's lymphoma. Other presentations include weight loss, chronic fever, chronic diarrhea and Candida infections.

Clinical features (Fig 8.12, Table 8.25) The clinical manifestations of AIDS can be grouped under four categories: 1) those caused by the direct effects of HIV; 2) opportunistic infections resulting from HIV-induced immunosuppression; 3) Kaposi's sarcoma; and 4) and other malignancies resulting from HIV-induced immunosuppression.

Direct effects of HIV infection

Acute HIV infection is occasionally associated with an infectious mononucleosis-like illness which typically develops between one to three months after exposure. It is characterised by the sudden onset of high grade fever, malaise, myalgias and arthralgia. Sore throat, diarrhea,

Table 8.25 1993 Revised CDC HIV Classification system and expanded AIDS surveillance definition for adolescents and adults

The revised system emphasises the importance of CD_4 lymphocyte testing in the clinical management of HIV infected persons. The system is based on 3 ranges of CD_4 counts and 3 clinical categories giving a matrix of 9 exclusive categories. The system replaces the 1986 classification.

Criteria for HIV infection: Persons 13 years or older with repeatedly (2 or more) reactive screening tests (ELISA) + specific antibodies identified by a supplemental test, e.g., Western blot

CLASSIFICATION SYSTEM	*Clinical category A*	*Clinical category B*	*Clinical category C**
CLINICAL CATEGORY CD_4 Cell Category A B C 1. ≥500/mm³ A1 B1 C1 2. 200–499/mm³ A2 B2 C2 3. <200/mm³ A3 B3 C3	Asymptomatic HIV infection Persistent generalised lymphadenopathy (PGL)[1] Acute (primary) HIV illness	Symptomatic, not A or C conditions. Examples include but not limited to: Bacillary angiomatosis Candidiasis, vulvovaginal: persistent >1 month, poorly responsive to Rx Candidiasis, oropharyngeal Cervical dysplasia, severe, or carcinoma in situ Constitutional symptoms, e.g. fever (>38.5°) or diarrhea > 1 month The above must be attributed to HIV infection or have a clinical course or management complicated by HIV.	Candidiasis: esophageal, trachea, bronchi Coccidioidomycosis, extrapulmonary Cryptococcosis, extrapulmonary Cervical cancer, invasive Cryptosporidiosis, chronic intestinal (> 1 month) CMV retinitis, or other than liver, spleen, nodes HIV encephalopathy Herpes simplex with mucocutaneous ulcer>1 month, bronchitis, pneumonia Histoplasmosis: disseminated, extrapulmonary Isosporiasis, chronic > 1month Kaposi's sarcoma Lymphoma: Burkitt's immunoblastic, primary in brain M.avium or M. kansasii, extrapulmonary M.tuberculosis, pulmonary or extrapulmonary Mycobacterium, other species disseminated or extrapulmonary Pneumocystis carinii pneumonia pneumonia, recurrent (≥ 2 episodes in 1 year) progressive multifocal leukoencephalopathy Salmonella bacteremia, recurrent Toxoplasmosis, cerebral Wasting syndrome due to HIV
	[1]Nodes in 2 or more extrainguinal sites, at least 1 cm in diameter for > 3 months		

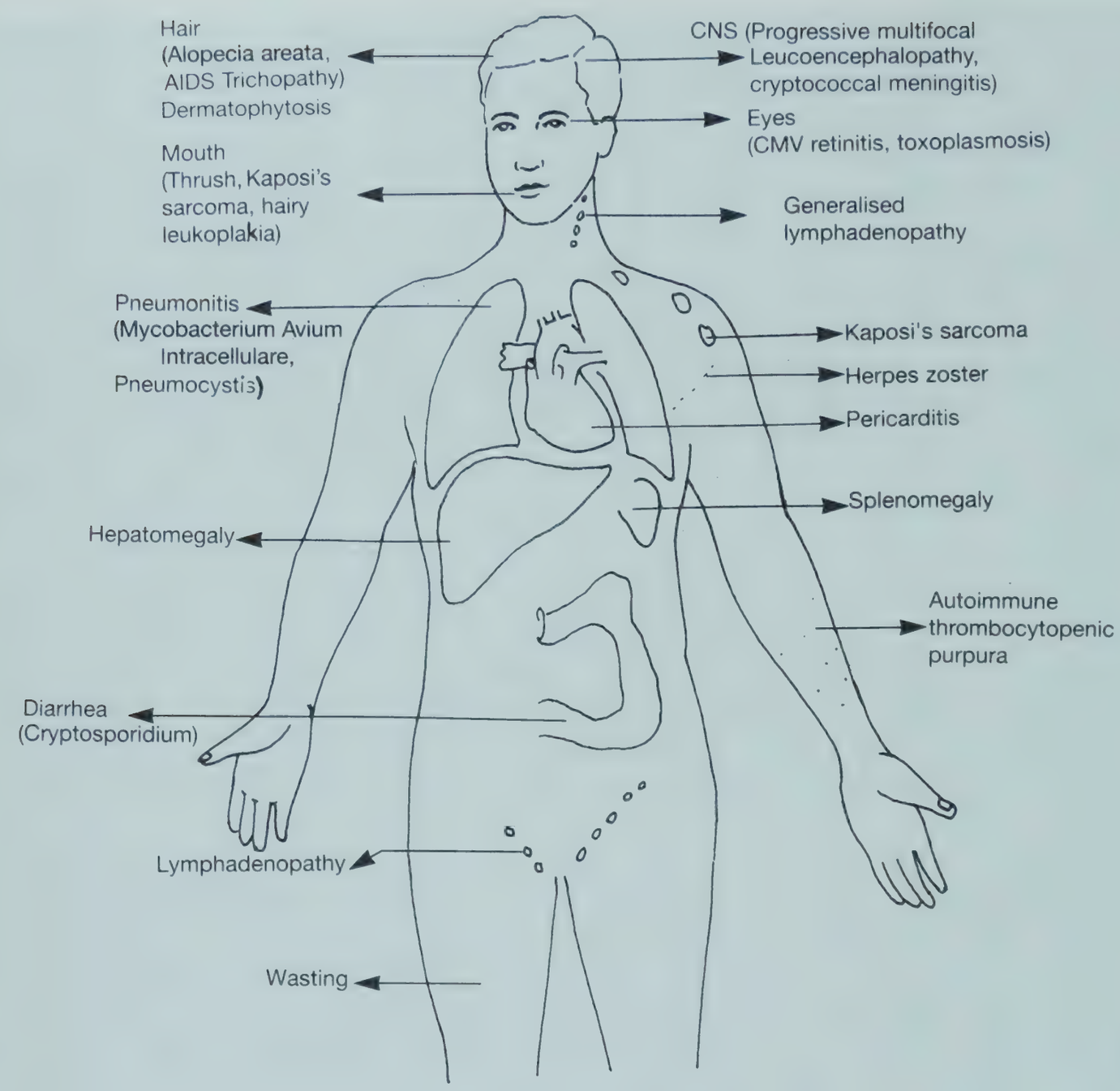


Fig 8.12 Clinical features of AIDS

generalised lymphadenopathy and a macular erythematous truncal eruption complete the clinical picture. A more common manifestation is the *persistent, generalised lymphadenopathy syndrome* (also called AIDS-related complex [ARC]). This condition is seen in 5–25 per cent of HIV-infected subjects. Fever and malaise are other prominent features of this syndrome. A severe form of ARC is the *Slim disease*; in this syndrome, seen in Africa and the tropics, there is severe wasting and weight loss. Roughly a quarter of ARC patients will progress to fullblown AIDS over the next year.

The most important direct clinical effects of HIV infection are on the central nervous system. The most important clinical syndrome is a subacute encephalitis (AIDS dementia complex) characterised by progressive dementia, psychomotor retardation, focal motor abnormalities, and behavioural changes. Clinical manifestations of this disorder are found in at least two-thirds of patients with AIDS. This disorder must be

distinguished from other infections of the central nervous system that are quite common in HIV-infected subjects and which can mimic this entity. In the list of differential diagnoses, central nervous system infections with Cryptococcus neoformans, Toxoplasma gondii, Treponema pallidum, and JC virus (progressive multifocal leukoencephalopathy) are noteworthy.

Various other systemic features include an enteropathy (characterised by malabsorption), a gastropathy (characterised by impaired gastric acid secretion), esophageal ulcerations and proctocolitis. Renal involvement[1] with HIV is suggested by the presence of protein in the urine. HIV infections of the heart can result in a dilated cardiomyopathy. A number of rheumatologic phenomena are associated with HIV infection: various types of arthritis, myopathies, a sicca syndrome (resembling Sjogren syndrome), and a syndrome mimicking systemic lupus erythematosus.

Opportunistic infections

Very often HIV infection is heralded by an opportunistic infection. Infection with the mycobacterial species is the most common secondary infection in AIDS patients in developing countries. The spread of tuberculosis is enhanced by the large number of infective bacteria which are present in the sputum of HIV-infected individuals with pulmonary tuberculosis. Multidrug-resistant organisms, and disseminated disease are very frequent in AIDS. It is not surprising, therefore, that these individuals respond poorly to chemotherapy and have a high mortality. M. avium-intracellulare infection is reported to be even more common than M. tuberculosis among AIDS patients. Evidence of disseminated M. avium-intracellulare infection can be found at autopsy in at least half of AIDS patients.

The most common opportunistic infection in AIDS patients in developed countries is Pneumocystis carinii pneumonia. The risk of pneumocystis infection increases markedly when the CD_4^+ T cell counts fall below 200/mm^3. Pneumocystis pneumonia usually manifests in these patients with the development of a non-productive cough followed by onset of progressive dyspnea. Typically, interstitial pneumonitis is evident on the chest X-ray, and arterial blood gas analyses reveal hypoxemia and hypercapnia. If the chest X-ray is negative but clinical suspicion is high, sputum examinations for pneumocystis should be obtained.

Other causes of recurrent opportunistic infections in AIDS patients include Candida (mucosal candidiasis), Histoplasma species, cytomegalovirus (disseminated CMV infection), Cryptococcus, and herpes viruses. Gastrointestinal pathogens can also cause recurrent severe disease; these include persistent diarrhea caused by Cryptosporidium or Isospora belli infection and bacteremia due to Salmonella species. Although AIDS patients frequently have infections due to unusual organisms, it must be remembered that they are also very prone to infection by conventional bacteria such as S. pneumoniae and H. influenzae (type b).

Syphilis is also a major problem in HIV-infected individuals. Tests for syphilis should therefore be obtained in all patients with newly diagnosed HIV infection; conversely, patients with newly-diagnosed syphilis should be tested for HIV. The issue is complicated by the observation that standard serologic tests for syphilis may be falsely negative in AIDS patients; a tissue biopsy and subsequent examination of the biopsy material for spirochaetes with special stains may be required. Furthermore, such patients may progress to neurosyphilis over a short interval of time despite penicillin therapy.

Kaposi's sarcoma

Approximately a third of AIDS patients present with Kaposi's sarcoma. Patients presenting with Kaposi's sarcoma generally have a less severe immune defect than patients presenting with an opportunistic infection. Classic Kaposi's sarcoma

[1] Kidney biopsies reveal a focal and segmental glomerulosclerosis.

in the non-AIDS subject has a cutaneous presentation and an indolent course. AIDS subjects have a florid form of the disease: skin lesions are multicentric, frequently the lymph nodes are affected and the visceral organs (especially the gastrointestinal tract) are infiltrated.

Other malignancies

HIV-infected individuals have an increased incidence of both non-Hodgkin's and Hodgkin's lymphoma.

Laboratory findings and diagnosis (Fig 8.13) The clinician faced with a patient with possible AIDS needs to follow a stepwise approach: 1) establish the diagnosis of HIV infection; 2) establish the diagnosis of AIDS; 3) assess prognostic indicators of the immunologic status of the HIV-infected patients to decide on optimal management strategies, and 4) seek and diagnose complicating infections and malignant disorders which are known to occur in patients with HIV infection.

Diagnosis of HIV infection The diagnosis of HIV infection does not by itself constitute a diagnosis of AIDS. HIV infection causes a continuum of manifestations, and the exact classification of a patient with HIV infection is *made on the basis of the clinical syndrome rather than on the basis of laboratory tests.*

The diagnosis of HIV infection is made with laboratory tests which measure antibodies to HIV. More than 90 per cent of patients with AIDS have antibodies to the virus and more than 90 per cent of asymptomatic carriers of the virus are antibody positive; therefore, anyone who is HIV-antibody positive should be assumed to have transmissible virus in his or her blood and body secretions. Thus, antibody testing is important for screening blood donors. Currently available ELISA tests, which measure antibody against HIV envelope antigens, have a sensitivity of 97 per cent and are about 99 per cent specific. Serum samples which are positive by ELISA in two consecutive assays are rechecked with a still more specific confirmatory test, usually the Western blot

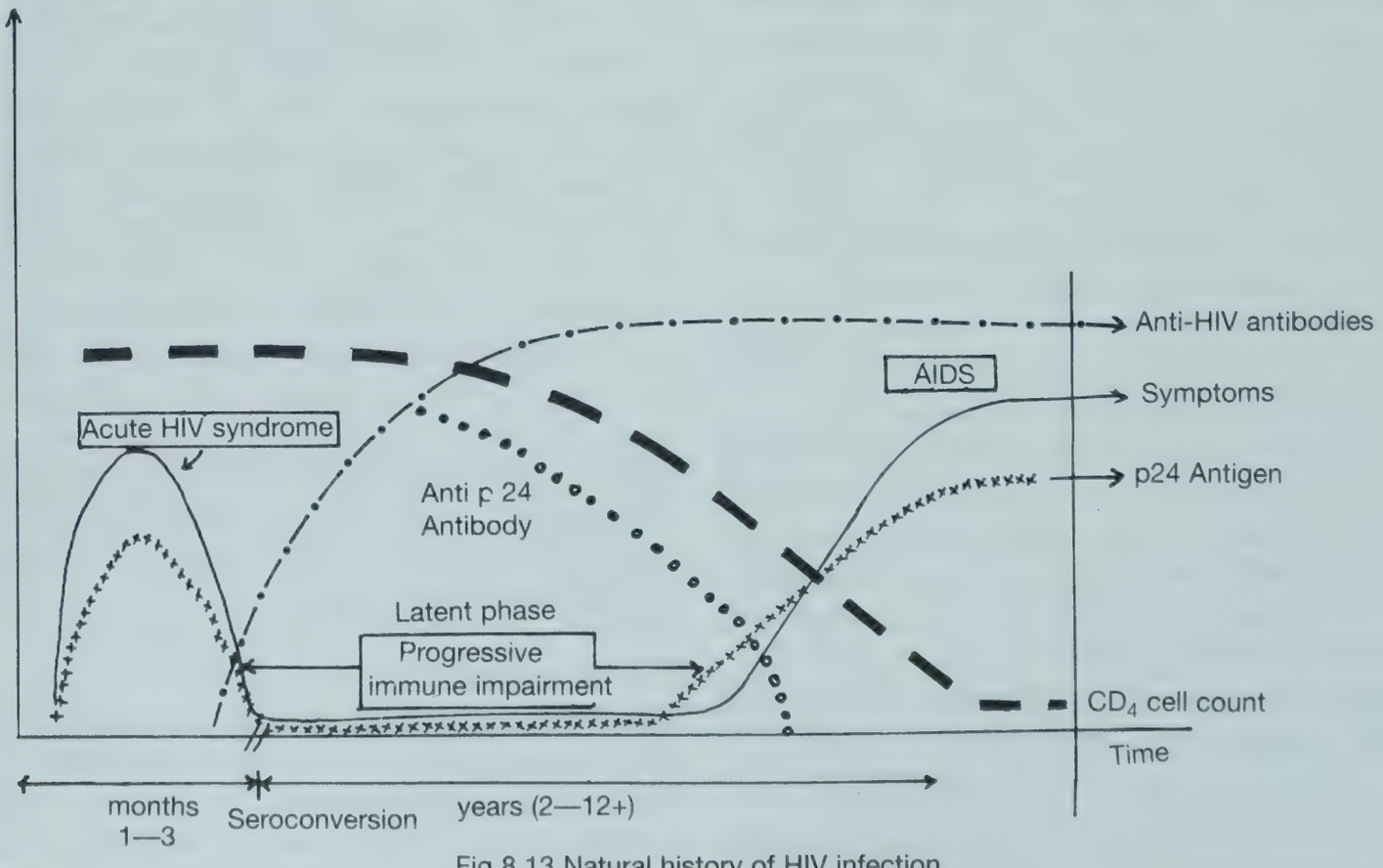


Fig 8.13 Natural history of HIV infection

assay.[1] In this technique the serum of the patient is evaluated for the presence of antibodies to specific HIV antigens. A positive test result generally requires the presence of antibody to two or more antigens. A negative test would not have antibodies to any of these antigens. All other patterns are regarded as indeterminate. In general, strongly positive or clearly negative ELISA tests will be confirmed by the Western blot assay, whereas weakly positive ELISA tests will be negative or indeterminate by Western blot testing. Typically, the conventional ELISA antibody tests become positive 1–3 months after infection with HIV, at approximately the same time that some patients experience the acute HIV-related infectious mononucleosis-like illness.

Diagnosis of AIDS and assessment of prognosis Laboratory markers to assess the prognosis for patients with HIV infection are being actively pursued. At present, the most accurate marker for disease progression is the serial measurement of the level of circulating CD_4^+ T cells; levels lower than 200/mm^3 are highly associated with disease progression.

Diagnosis of complicating infections Because patients with AIDS are very prone to opportunistic infections, these must be carefully sought and aggressively treated. For instance, the presence of pulmonary infiltrates warrants an examination of the sputum followed by bronchoalveolar lavage (if the sputum examination is inconclusive), or a biopsy; central nervous system symptoms indicate a need for obtaining a CT scan of the head and/or a spinal tap. Diarrhea should be investigated with culture and examination of stools for parasites.

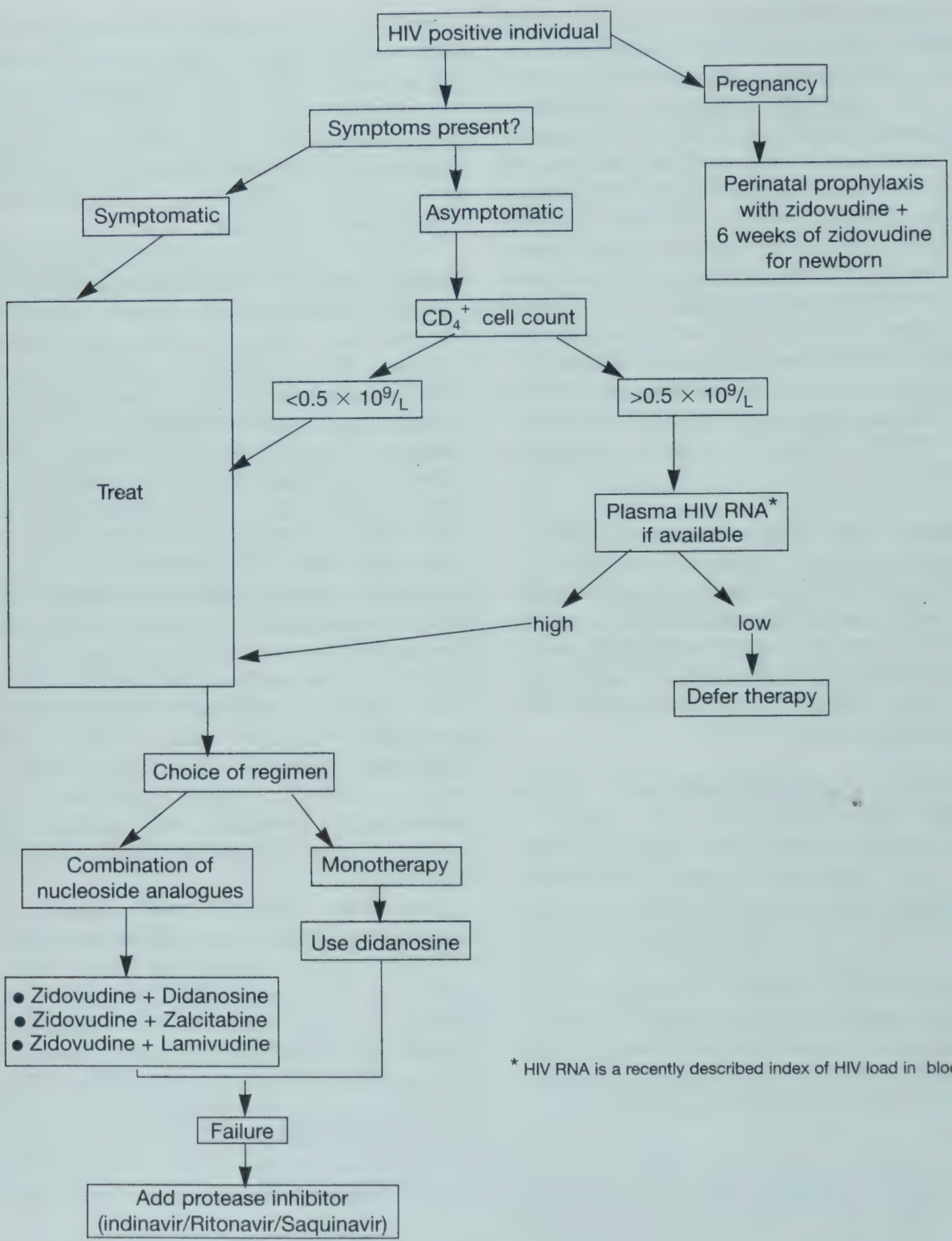
Management Prevention of HIV spread is one of the cornerstones of therapy. Health education programmes which educate the public about safer sexual practices are essential. The risk of HIV transmission in the healthcare setting is extremely low.[2] Emphasis should be placed on the application of universal precautions within the hospital environment.

Therapy for patients with AIDS consists of treatment aimed at the HIV infection itself and treatment aimed at the secondary infections and malignant disorders associated with HIV infection. The cornerstone of anti-HIV therapy upto the present has been zidovudine (also known as AZT), a nucleoside analogue which blocks HIV replication by inhibiting HIV reverse transcriptase (Fig 8.14). Other drugs with a similar effect are 2',3'-dideoxycytidine (also known as ddC) and 2',3'- dideoxyinosine (also termed ddI, or didanosine). These drugs reduce the spread of HIV to uninfected cells. They do not affect viral replication within chronically infected cells, and have only a modest effect in reducing the concentration of HIV in semen (an important factor in the sexual transmission of the virus). Despite these limitations, zidovudine has been shown to improve survival, improve neurologic and immunologic function, and reduce the severity of opportunistic infections in patients with AIDS.

Zidovudine (500 to 600 mg/day) is administered orally, often with erythropoietin, GM-CSF, which reduces its bone marrow toxicity. However, the benefits of zidovudine therapy appear to decrease with time. Ganciclovir is used in AIDS patients who have cytomegalovirus retinitis and a combination of α-interferon and zidovudine is used in AIDS patients with Kaposi's sarcoma. Trimethoprim-sulfamethoxazole, given in a dosage of one double-strength tablet (160 mg of trimethoprim

[1] In the Western blot assay, a lysate of HIV-1 is separated into its individual protein components by polyacrylamide gel electrophoresis. These proteins are transferred onto nitrocellulose paper and then exposed to the patient's serum. Any antibody that adheres to a protein band can be detected by an antihuman IgG antibody that in the presence of a substrate yields a colour reaction.

[2] The rate of transmission is less than 0.5 per cent after direct inoculation of infected blood through a needle-stick injury.



* HIV RNA is a recently described index of HIV load in blood.

Fig 8.14 Antiretroviral therapy of HIV postive individual

and 800 mg of sulfamethoxazole) twice a day, is indicated in HIV-infected individuals with CD_4^+ T cell counts lower than 200/mm^3 to provide prophylaxis against Pneumocystis pneumonia; aerosolised pentamidine (300 mg administered once every four weeks) for prophylaxis is an effective alternative with fewer adverse effects.

INFECTIONS DUE TO ENTEROVIRUSES

Enteroviruses are a group of RNA viruses which inhabit the gastrointestinal tract and include the *Coxsackie, echo*[1] and *polio viruses.* The enteroviruses and the rhinoviruses together constitute the *Picorna virus family.*

[1] Standing for enteric cytopathogenic human orphan

Diseases due to Non-Polio Enteroviruses

Etiology The non-polio enteroviruses are RNA viruses which include 23 group A Coxsackie viruses (A1–A24, except A23), 6 group B Coxsackie viruses (B1–B6), 31 echoviruses (types 1–33, except types 10 and 28), and 4 enteroviruses (types 68-71).

Epidemiology Humans are the only known natural hosts of enteroviruses. Enteroviruses are ubiquitous and spread by the feco-oral and droplet method. Young children, people of lower socioeconomic status and those living under poor hygienic conditions are more predisposed. There is no seasonal pattern evident in tropical countries, although in temperate countries there is a peak in summer.

Table 8.26 Disease syndromes caused by non-polio enteroviruses

Syndrome	*Serotype implicated*	*Age-group affected*	*Clinical features*
A. **Respiratory**			
1. Herpangina	Coxsackie A2, 4–6, 8, 10, 16, 23	infants and children	vesicular lesions on soft palate, fauces, throat; fever, pain on swallowing
2. Pharyngitis	Coxsackie A21, B1–5, Echo 4, 8, 20	infants	fever, throat congestion
B. **Musculoskeletal**			
Epidemic pleurodynia (Bornholm disease)	Coxsackie B1–6	children	fever, pleuritic chest pain, myalgias, malaise, sore throat
C. **Cardiac**			
Myopericarditis	Coxsackie B1–5	any age, especially neonates	fever, feeding difficulties, tachypnea, tachycardia
D. **Gastroenteritis**			
Diarrhea	Echo 6, 14, 18	neonate	acute diarrhea
E. **Ocular**			
Conjunctivitis	Enterovirus 70, Coxsackie A24, Echo 7	any age	hemorrhagic conjunctivitis
F. **Nervous system**			
Aseptic meningitis	Coxsackie A2, 4, 7, 9, 23	infants and young children	headache, fever, neck stiffness, vomiting
G. **Skin**			
Hand-foot-mouth disease	Coxsackie A16	young children	vesicular exanthem over hands, feet and buccal mucosa, palate

Clinical features The clinical syndromes caused by the enteroviruses are enumerated in Table 8.26.

Diagnosis Enteroviruses can persist in the feces for as long as 8 to 12 weeks; hence, in addition to fecal isolates, a rising titre of antibodies in serum required for a definitive diagnosis.

Treatment There is no specific treatment for enteroviral infection. Supportive measures are indicated in the form of antipyretics for fever, decongestants for rhinitis, and antidiarrheal drugs for gastroenteritis.

Poliomyelitis

Polio is an acute infection due to a neurotropic virus with special affinity for the anterior horn cells of the spinal cord and is characterised by fever and motor paralysis.

Epidemiology Poliomyelitis is widespread in the tropics. Children of both sexes below the age of 5 years are predominantly affected. Epidemics of the disease occur in late summer and autumn. Where sanitary conditions are poor, the disease is endemic and cases are reported all year round. Tonsillectomy and pregnancy have been reported to predispose to a paralytic form of illness. An association with intramuscular injections (for an unrelated illness during epidemics) and clinical poliomyelitis has been suggested. Surveys in our country suggest an annual incidence rate of paralytic poliomyelitis of about 20 per 100,000 with an estimated 150,000 new cases yearly. Vaccination has dramatically reduced the occurrence of paralytic poliomyelitis.

Pathogenesis and pathology Polio viruses are of three types (I,II,III), of which type I is the most likely to result in paralytic disease. Unapparent infections outnumber symptomatic infections by a ratio of 100:1, and are the main source of polio virus spread. The incubation period is 6–15 days (usually 1–2 weeks) and infectivity is maximum during the first week of illness. The virus is excreted in the stools for several weeks. The virus spreads by the droplet method, with the portals of entry being the upper respiratory tract and the gastrointestinal tract. The virus replicates in the lymphoid tissue of the tonsils, pharynx and the Peyer's patches. A primary viremia is then initiated by which the virus spreads to receptor-bearing target tissues. A second phase of replication occurs in the target tissues resulting in symptoms and a secondary viremia.

The polio virus recognises a receptor expressed on the anterior horn cells of the spinal cord, dorsal root ganglia, motor neurons, skeletal muscle and lymphoid tissues. The spinal cord is the most often affected, with the cervical and lumbar swellings of the cord being most involved affected. In the anterior horn, ganglion cells show degeneration, necrosis, foci of lymphocytic infiltration and hemorrhages. Large motor cells in the grey matter of the brainstem can be attacked by the virus; large pyramidal cells of the cerebral motor cortex can be affected but the white matter is spared. The severity of clinical illness is determined by the extent and distribution (spinal versus bulbar) of neuronal infection.

Clinical features Polio virus infection may be one of four types:

1. Asymptomatic infections (90%) outnumber symptomatic infection. The virus replicates in the gut and is excreted in the stools and serves as a source of infection for the non-immune.
2. Abortive poliomyelitis (5%), also called a minor illness, is a non-specific, febrile illness characterised by fever, headache, malaise, sore throat and diarrhea.
3. Non-paralytic poliomyelitis (1–2%) takes the form of an aseptic meningitis. Besides the features mentioned above, signs of meningeal irritation and muscle spasms may occur.

4. Paralytic poliomyelitis (0.1–2%), also called the major illness, is the most severe form of the disease. The initial phase of pre-paralytic illness is dominated by symptoms which suggest a flu-like illness. An important sign, which may sometimes be present, is the presence of hyperesthesia of the affected muscles. The muscles are extremely tender to touch and jerky involuntary movements may be present. The paralytic stage is usually sudden in onset and characterised by flaccid paralysis which increases to a maximum within 72 hours.

In the spinal form of the disease, asymmetrical weakness of one or more limbs develops. The parts affected in order of frequency are: legs, arms, back, thorax and diaphragm. Paralysis of a lower extremity is common; the extensors of the hip, knee and dorsiflexors of the ankle are the most affected muscles. In the upper extremity, the shoulder girdle muscles are affected more severely. Paralysis of the intercostal muscles and the diaphragm results in reduced chest expansion and a diminished vital capacity. Paralysis is associated with absent tendon reflexes. Cutaneous sensation is preserved. The sphincters are usually spared.

The bulbar form of the disease is infrequent. In this condition there is rapid onset of facial, ocular and lower cranial nerve palsies. Involvement of the lower cranial nerves is associated with dysphagia, dysphonia, nasal regurgitation and the threat of respiratory paralysis due to the involvement of brainstem respiratory centres.

Investigations The peripheral blood findings are generally unremarkable. Neutralising antibodies appear during the second week of illness. An examination of the CSF may show normal glucose levels, normal or slight increase in protein levels and a mononuclear pleocytosis (< 500 cells/mm^3).

The differential diagnosis includes the Landry-Guillain-Barre (LGB) syndrome and other causes of acute motor paralysis (discussed in detail under the neurology section). Favouring a diagnosis of the LGB syndrome include a lack of fever, a more symmetrical and ascending pattern of weakness, progression of weakness for over 5 days of illness, presence of sensory symptoms, sphincter involvement and elevation of CSF proteins without concomitant pleocytosis.

After the acute course of illness, the patient may have a localised wasted limb (post-polio residual paralysis). Years later, when the acute episode is no longer clearly remembered, the disorder must be differentiated from juvenile motor neuron disease.

Treatment There is no specific therapy to reverse or prevent progression of motor weakness. The treatment is mainly supportive and includes clinical vigilance to detect complications such as the involvement of cranial nerves or respiratory muscles. In the acute stage of the paralytic illness, rest in bed has been recommended. The paralysed extremity must be kept in a position of relaxation using pillows, sandbags or celluloid splints. In the cases of respiratory muscle weakness, assisted respiratory care may be required. After the progression of paralysis has ceased, physiotherapy is begun to prevent contractures and deformities.

Prognosis In the spinal form of the disease, about 15 per cent of patients recover completely without residual weakness. Another 30 per cent have near-complete recovery of motor weakness. About 45 per cent of patients are left with a motor deficit. These patients may have permanent residues such as a short or wasted extremity, deformities (such as talipes, flexed knee, scoliosis) due to unopposed action of the normal antagonist muscles, and vasomotor changes (a slightly 'colder' limb). Mortality of the spinal form of disease is about 2–9 per cent. Motor recovery is dramatic by three weeks, although it may continue for about 6 months

after the acute episode. Mortality of the bulbar form of the disease is reported to be 50 per cent.

Prevention Poliomyelitis is a preventable disease. Two effective forms of vaccination are available: the oral Sabin vaccine (live attenuated strain) and the injectable Salk vaccine (inactivated virus). All immunocompetent infants must be vaccinated in the first year. At least three doses of the oral vaccine are recommended (6–8 weeks apart) with a booster dose at about 15–18 months. In immunodeficient infants, the inactivated vaccine is preferable.

DISEASES DUE TO RHINOVIRUSES

Rhinoviruses are the most common cause of the common cold (*acute coryza*) and upper respiratory tract infections. More than 100 serotypes are recognised which explains the occurrence of multiple episodes throughout life.

Pathogenesis Rhinoviruses are acquired either by droplet infection (from aerosols) or by means of fomites; transmission from person to person, probably through hands, seems to be a more important mode of transmission than the aerosol route. The viruses multiply in the nasal mucosa. The rhinoviruses share a receptor which is called *intercellular adhesion molecule type 1 (ICAM-1).* ICAM-1 is a member of the immunoglobulin supergene family and is expressed on epithelial cells, fibroblasts and B lymphoblastoid cell lines. Viral replication results in the release of inflammatory mediators such as bradykinin and histamine; these mediators account for the 'running nose'. Immunity develops due to mucosal IgA synthesis, but wears away about 18 months after the infection.

Clinical features About half of all rhinovirus infections are subclinical. Two yearly peaks are seen; one in the autumn and another in late spring. Young children are believed to be the primary vector. Common cold symptoms caused by rhinoviruses are indistinguishable from those caused by other agents (paramyxo-, entero- and coronaviruses). Infection manifests initially with frequent sneezing followed by rhinorrhea. Nasal discharge is watery initially, but can become mucoid-mucopurulent. Mild pharyngitis often accompanies the illness. Fever, if present, is of a mild degree. The illness runs a self-limited course of 4–7 days.

Diagnosis The presence of high fever or severe systemic symptoms suggests an influenza-like illness. The presence of a pharyngeal exudate or unilateral painful cervical adenopathy suggests bacterial infection. In such cases a throat swab may be obtained for bacterial cultures. Usually the clinical syndrome is so characteristic and the number of causative viruses so diverse that no specific investigation is required, especially as no specific treatment is effective.

Treatment Treatment of rhinovirus infection is symptomatic. A warm environment is recommended, and steam inhalations used in case the nose is 'stuffy' and blocked. Antihistamines may provide symptomatic relief. Since rhinoviruses spread by person to person contact through contaminated secretions on fingers, it is recommended that hands are washed frequently by affected individuals.

DISEASES DUE TO ADENOVIRUSES

Adenoviruses are DNA viruses that cause acute self-limiting febrile illnesses characterised by inflammation of the respiratory and ocular mucosa and hyperplasia of submucosal and regional lymph nodes.

Epidemiology Adenoviruses can infect adults and children alike, although different serotypes have a differential propensity to infect various age groups. The transmission of adenovirus is by

Table 8.27 Spectrum of diseases caused by adenoviruses

Syndrome	*Serotype implicated*	*Age-group affected*	*Clinical features*
A. **Respiratory**			
1. Acute febrile respiratory illness	1–3, 5, 6	children	fever, pharyngitis, tracheitis, bronchitis
2. Acute respiratory disease	4, 7	adults	malaise, fever, chills, headache, pharyngitis, dry cough
3. Viral pneumonia	4, 7	adults and children	high fever, rash, lobular pneumonia
B. **Ocular**			
Epidemic keratoconjunctivitis	8	adults	red eye, edema, periorbital swelling, superficial opacity of cornea without ulceration
Acute follicular conjunctivitis	3, 7	adults	unilateral mucoid discharge, foreign body sensation, preauricular lymphadenopathy
C. **Combined respiratory and ocular**			
Pharyngoconjunctival fever	3, 4, 7	children (especially after swimming in lakes)	spiking fever, pharyngitis, conjunctivitis, cervical adenitis
D. **Bladder**			
Hemorrhagic cystitis	11	children (boys)	hematuria, dysuria, frequency

the feco-oral, droplet route or by means of direct inoculation. The incubation period is usually less than one week.

Clinical features The various clinical syndromes caused by adenoviruses are listed in Table 8.27.

Diagnosis Adenovirus infection may be indistinguishable from other viral infections of the upper respiratory tract. A definitive diagnosis requires isolation of the virus from respiratory, fecal or ocular secretions. A fourfold rise of antibody titres also indicates recent infection.

Treatment Treatment is mainly symptomatic and consists of antipyretics and analgesics. Topical corticosteroids may relieve the symptoms and shorten the course of epidemic keratoconjunctivitis.

DISEASES DUE TO ARBOVIRUSES

Chikungunya

Chikungunya[1] is a mosquito-borne disease caused by an arbovirus belonging to the alphavirus genus, and is characterised by severe joint pains, rash and fever.

[1] The name is derived from the Swahili and means 'that which bends back', a reference to the severe joint pains.

Epidemiology The chikungunya virus is endemic in parts of Africa and southeast Asia. There is a forest cycle where the virus is maintained as a zoonosis and an urban cycle involving human to human transmission by the mosquito *Aedes aegypti.* Children under 10 years are predominantly affected as almost all adults acquire immunity.

Pathology and etiopathogenesis Joints are predominantly affected by the disease and there is pathological evidence of synovitis with pannus formation. The skin rash is related to the vasculitic damage of dermal capillaries.

Clinical features The onset of disease is typically abrupt after an incubation period of about 3 to 6 days. The predominant symptoms are pain and swelling of the wrist and ankle joints, along with involvement of the small joints of the hands and feet. The fever is high grade and often biphasic with an apyrexial period of 2 to 3 days in between. Headache, myalgias and symptoms of upper respiratory tract inflammation (sore throat with cervical adenopathy) are common. The typical rash evolves towards the end of the first week of illness, is maculopapular and involves the trunks and the extensor surfaces of the extremities. The disease runs a self-limited course of 7 to 10 days. Residual arthralgias or joint stiffness may be seen occasionally. Bleeding complications are seldom seen and include a hemorrhagic rash and skin petechiae.

Diagnosis Specific diagnosis of the disease requires the demonstration of a rise in specific antibody titre in the blood. Dengue fever is to be considered in the differential diagnosis; headache, retro-orbital pain and lumbosacral pain are more frequent in dengue fever, whereas conjunctival infection and the abrupt onset of joint involvement favour a diagnosis of chikungunya.

Treatment Treatment is symptomatic and consists of antipyretics for fever and anti-inflammatory agents for the relief of joint pains.

Prevention Prevention of the disease is primarily achieved by control of the mosquito vector with aerial or ground sprays.

Kyasanur Forest Disease

Kyasanur Forest Disese (KFD) is a severe disease caused by a tick-borne arbovirus belonging to the *fla i irus* complex and is characterised by fever, rash and, often, neurologic signs.

Epidemiology The disorder was first described in the forest areas of the Shimoga district of Karnataka and is restricted in distribution to this state. The disease is caused by a virus transmitted from monkeys, small mammals and cattle to humans by a tick, *Haemophysalis spinigera.* Adult males who enter the forest areas are predominantly affected and the disease does not spread from person to person. The outbreaks are focal and often coincident with deforestation and implementation of agricultural projects. There is a seasonal variation, with peak incidence reported in the pre-monsoon months of February to April.

Pathology The disease is characterised by generalised hemorrhage, reticuloendothelial cell hyperplasia, paraenchymal degeneration observed in the liver and kidneys, and a hemorrhagic pneumonitis.

Clinical features There is an incubation period of 4 to 7 days after the tick bite prior to the onset of clinical features. Fever, headache, severe back pain and pain in the extremities herald the onset and the patient is prostrate. Conjunctival suffusion, generalised lymphadenopathy and cough are prominent manifestations. The disease is often biphasic, with features of a mild meningoencephalitis dominating the second

phase which typically begins after a week of the illness. Hemorrhagic complications may occur at any time during the clinical course and include epistaxis, hemoptysis, hematemesis and genitourinary bleeding. The majority of patients recover uneventfully after 7 to 12 days.

Diagnosis A history of travel to the area should arouse suspicion of the disease. The observation of an excess death rate of macaque monkeys in the forest should lead to the suspicion of the outbreak of the disease in the forest. Specific diagnosis requires the demonstration of a rising titre of antibodies in patient's sera.

Treatment The treatment is symptomatic and includes the administration of antipyretics and maintenance of adequate hydration. The case-fatality rate is between 5 and 10 per cent.

Prevention Persons working in the forest area should use a tick repellant. A formalinised tissue culture vaccine has been developed and appears safe and effective.

Japanese Encephalitis

Japanese encephalitis[1] is an acute mosquito-borne infection of the central nervous system which is caused by an arbovirus belonging to the *Flavivirus* genus.

Epidemiology Japanese encephalitis is endemic in Southeast Asia. Epidemics of the disease have been observed in northeast India; one such outbreak in 1978 affected thousands of people. The disease is predominantly rural in distribution and men are affected more often than women. All age groups are susceptible, though the severity of the illness is often more in the very young and the very old. The disease is caused by a virus transmitted by the mosquito *Culex 'vishnui' complex* in India. Humans are accidental hosts. The natural cycle of illness affects wild birds and swine that abound in paddy fields, the breeding ground of the *Culex* species.

Pathology Once the virus has been introduced into the body by the bite of the mosquito, it initially replicates in the extraneural tissues. A viremia ensues and the virus crosses the blood-brain barrier and causes encephalitis of a varying degree. The brain appears congested, edematous and there may be focal areas of hemorrhage. There is widespread neuronophagia with neuronal degeneration which especially affects the cerebral cortex, the basal ganglia and the Purkinje cells of the cerebellum. A perivascular infiltrate with mononuclear cells is usually present.

Clinical features Most infections with the Japanese encephalitis virus are asymptomatic; the ratio of subclinical to clinical infection has been reported to be 30:1. The incubation period extends from 4 to 14 days. The clinical spectrum ranges from a mild aseptic meningitis to a severe meningoencephalitis. The initial phase of the illness may be dominated by gastrointestinal and respiratory symptoms. The neurologic illness is characterised by severe headaches, impaired consciousness, muscular rigidity, ataxia and involuntary movements, cranial nerve palsies and pathologic reflexes. Usually the fever resolves in 7 to 10 days followed by resolution of the neurologic signs. Residual neurologic deficits may be seen in upto 25 per cent of patients and include mental impairment, extrapyramidal syndromes, motor paralysis and autonomic disturbances.

Diagnosis Detection of antibodies in the sera or the CSF by ELISA is diagnostic of the illness. The peripheral blood may show a mild neutrophilic leucocytosis. The CSF has a lymphocytosis (usually < 500 cells/mm^3) and the protein content is elevated.

[1] The term Japanese B encephalitis was earlier used to distinguish it from the type A encephalitis (von Economo's encephalitis) that occurred in 1924.

Treatment Treatment is mainly supportive. Convulsions are frequent in children and may require treatment with anticonvulsant drugs. The patient is monitored for cardiorespiratory complications.

Prevention Preventive measures include the use of antimosquito campaigns, agricultural pesticides and changes in agricultural practices and pig husbandry. A commercial vaccine is available and has been shown to be effective in China and Japan.

Dengue (Break bone fever)

Dengue is a febrile human illness caused by a group B arbovirus and is transmitted by the mosquito *Aedes aegypti.* Dengue virus is a flavivirus which is morphologically indistinguishable from the yellow fever virus. The virus has four serotypes, of which Type 4 occurs most frequently in Asia.

Epidemiology Dengue is endemic in south-east Asia, and in some parts of Central and South America. The disease is more common in urban areas with large rainfall. Humans are the primary reservoirs and mosquitoes transmit the virus from infected humans to non-infected humans.

Clinical features Dengue virus primarily causes two types of illness in humans: classical dengue fever and dengue hemorrhagic fever. Dengue fever, the more common illness, is a mild febrile illness of children characterised by the triad of abrupt onset of moderate to high fever, severe frontal or retroorbital headache and a rash. The disease is more severe in adults. The incubation period is approximately 5 to 8 days. The illness often takes a biphasic course, with an afebrile period interspersed between two febrile phases (saddle-back pattern of fever). Severe backache, myalgias, and pain in the extremities (so-called bone pain) are important features of dengue fever. An evanescent, maculopapular rash may be seen and is occasionally followed by a morbilliform, scarlatiniform, or petechial eruption which spreads from the trunk to the extremities. Posterior cervical, epitrochlear and inguinal lymph nodes are frequently enlarged. Dengue fever has a self-limited course of about 5 to 7 days.

Dengue hemorrhagic fever (DHF) is the less common but more serious form of the disease. It is seen mainly in Southeast Asia and is more common in children below the age of 10 years. Immunological mechanisms have been implicated in the pathogenesis of this syndrome. The disorder is characterised by a febrile illness with a variety of bleeding manifestations; skin petechiae, purpura, gingival oozing, epistaxis, gastrointestinal bleeding, and hematuria can occur. Profound hemorrhage can result in peripheral circulatory collapse and shock. Hepatomegaly is common but arthralgia and myalgia are unusual (unlike classical dengue fever). The diagnostic criteria for DHF are: 1) a positive tourniquet test (20 or more petechiae per square inch); 2) hemoconcentration manifested as an increase in hemato-crit of 20 per cent or more; 3) thrombocytopenia associated with a platelet count of less than 100,000/mm^3; and 4) hypotension with a pulse pressure of less than 20 mmHg. When hypotension is present, the term *dengue shock syndrome* is also used.

Investigations Dengue is diagnosed by viral isolation as well as by serologic techniques involving complement fixation, hemagglutination inhibition, and neutralising antibodies. The diagnosis can also be established by a polymerase chain reaction test. The total blood leukocyte count shows leukopenia in classical dengue fever. Leukocytosis is more common in DHF.

Treatment The treatment of both dengue fever and DHF is symptomatic. Fever responds well to non-aspirin[1] antipyretics. Patients with dengue

[1] Aspirin is contraindicated in DHF.

hemorrhagic fever additionally require blood transfusions, along with repletion of fluids and electrolytes. If there is evidence of disseminated intravascular coagulation, heparin may be used cautiously. High-dose methylprednisolone treatment has not been effective in the management of established shock. Mortality due to DHF ranges from 5 to 30 per cent, with the higher rate being reported in infants.

RUBELLA (GERMAN MEASLES)

Rubella is an acute, mildly contagious disease characterised by a 'three-day' rash and lymphadenopathy.

Epidemiology The rubella virus is an RNA virus of the *Toga virus* family. Adolescents and children between the ages of 5 and 9 years are affected most often. The disease is spread through droplets from an infected person; the period of infectivity ranges from one week before to 4 days after the appearance of the rash.

Clinical features The incubation period is about 18 days (range 14–21). At onset there may be malaise and fever which culminates in a rash. The rash begins on the face and is maculopapular and 'rose-pink'. It rapidly spreads to the trunk and extremities and generally disappears by the third day. Small red petechial macules (*Forchheimer spots*) may appear on the soft palate. Tender swelling of the suboccipital, postauricular and postcervical lymph nodes is a hallmark of rubella. Polyarthralgia or polyarthritis may be an important feature in young women.

Complications Maternal rubella can lead to congenital birth defects in the babies; about 50 per cent of women infected in the first trimester, 20 per cent of those infected in the second trimester and 5 per cent of those infected in the third trimester, will produce infants with congenital defects. Infections in the first trimester may also lead to spontaneous abortions. The congenital rubella syndrome is characterised by cataracts, deafness and cardiac defects (patent ductus arteriosus, septal defects). Mental retardation, low birth weight and microcephaly are common associated manifestations. The term '*expanded rubella syndrome*' is used to refer to the above manifestations along with other less common features linked to the rubella virus, that is, thrombocytopenic purpura, hepatosplenomegaly, interstitial pneumonitis, myocarditis and metaphyseal bone lesions.

Diagnosis The clinical picture of a febrile illness associated with a rash and lymphadenopathy in a child is suggestive of rubella but definite confirmation requires either isolation of the virus or serologic tests (IgM specific antibodies).

Treatment There is no specific treatment. Supportive measures include antipyretics for fever and antiinflammatory agents for arthritis.

Prevention Rubella is a preventable disease. Active immunisation with a live-attenuated strain of the virus is recommended in children at the age of 15 months (usually in combination with measles and mumps as MMR). A booster dose (rubella alone) is sometimes given to girls between 10 and 13 years.

RABIES (HYDROPHOBIA)

Rabies is an acute fatal disease of the nervous system due to a neurotropic virus which is communicated to humans through the bites (or licks on abraded skin) of infected animals.

Epidemiology Rabies is due to a bullet-shaped virus belonging to the rhabdovirus family. Rabies is a zoonosis. Animals (dogs, wolves, racoons and bats) are the common vectors of disease. Humans are infected by the inoculation of virus contained in the saliva of the animal as a result of an animal bite. Rarely, corneal transplantation from an infected dying patient has lead to the transmission of rabies. The naturally occurring strain (*street virus*) of the

virus has a long and variable incubation period. Wounds on the face (60% risk) and hands (15–40% risk) are especially likely to be infective due to the richness of nerve endings. Punctures and lacerated wounds are particularly dangerous. Clothes worn by the victim of a bite provide some protection from the disease.

Pathogenesis and pathology The rabies virus is confined to the site of inoculation for about 4 hours after which it enters the nervous system through muscle spindles in striated muscles. It travels along the nerves at a rate of 3 mm/hour to reach the central nervous system. The virus replicates in the brain tissue. The brain shows congestion, punctate hemorrhages and perivascular lymphocytic infiltration. Inclusion bodies called *Negri bodies* are abundant in the hippocampus area of the brain. The characteristic spasms of illness occur due to the reflex irritability of the deglutition and respiratory centres. From the brain, the virus may travel to other tissues, especially through efferent nerves to the salivary glands and into the saliva.

Clinical features After an incubation period of 40–60 days (range 12 days to 2 years), the disease may begin with a feeling of pain and irritation near the site of the bite. This prodromal phase is also characterised by photophobia, sensitivity to loud noises, tachycardia, excessive salivation and pupillary dilatation. After 2 to 10 days, the second phase of the disease (phase of excitation) begins. The cardinal manifestations of this phase are muscular spasms. The laryngeal and respiratory muscles are the first affected. Laryngeal spasms are provoked by any attempt to drink water, and sometimes by even the mention of water (hence, 'hydrophobia'). Spasms later become more generalised. Between spasms, the patient is mentally clear. Fever is common. This phase is also associated with ocular palsies, asymmetric pupils, absent corneal reflexes, facial muscle weakness and hoarseness of voice. Spasms soon give way to paralysis which may take different patterns such as ascending paralysis, hemiplegia, or myelitis. The above pattern of illness is termed *furious* rabies to distinguish it from *dumb* rabies (20 per cent patients, especially after exposure to rabid bats), in which there is only paralysis without any spasms. The generalised flaccid paralysis soon culminates in peripheral vascular collapse, coma and death.

Diagnosis The diagnosis of rabies is based on detection of the rabies antigen by the indirect immunofluorescence of brain, skin or corneal smears. The fluorescent antibody test is the serologic test of choice. Dogs or cats should be kept under observation for 10 days. If the animal is alive at the end of this period, it is not rabid. If the animal dies during the period of observation, an autopsy should be performed to examine the brain using direct immunofluorescence.

Treatment

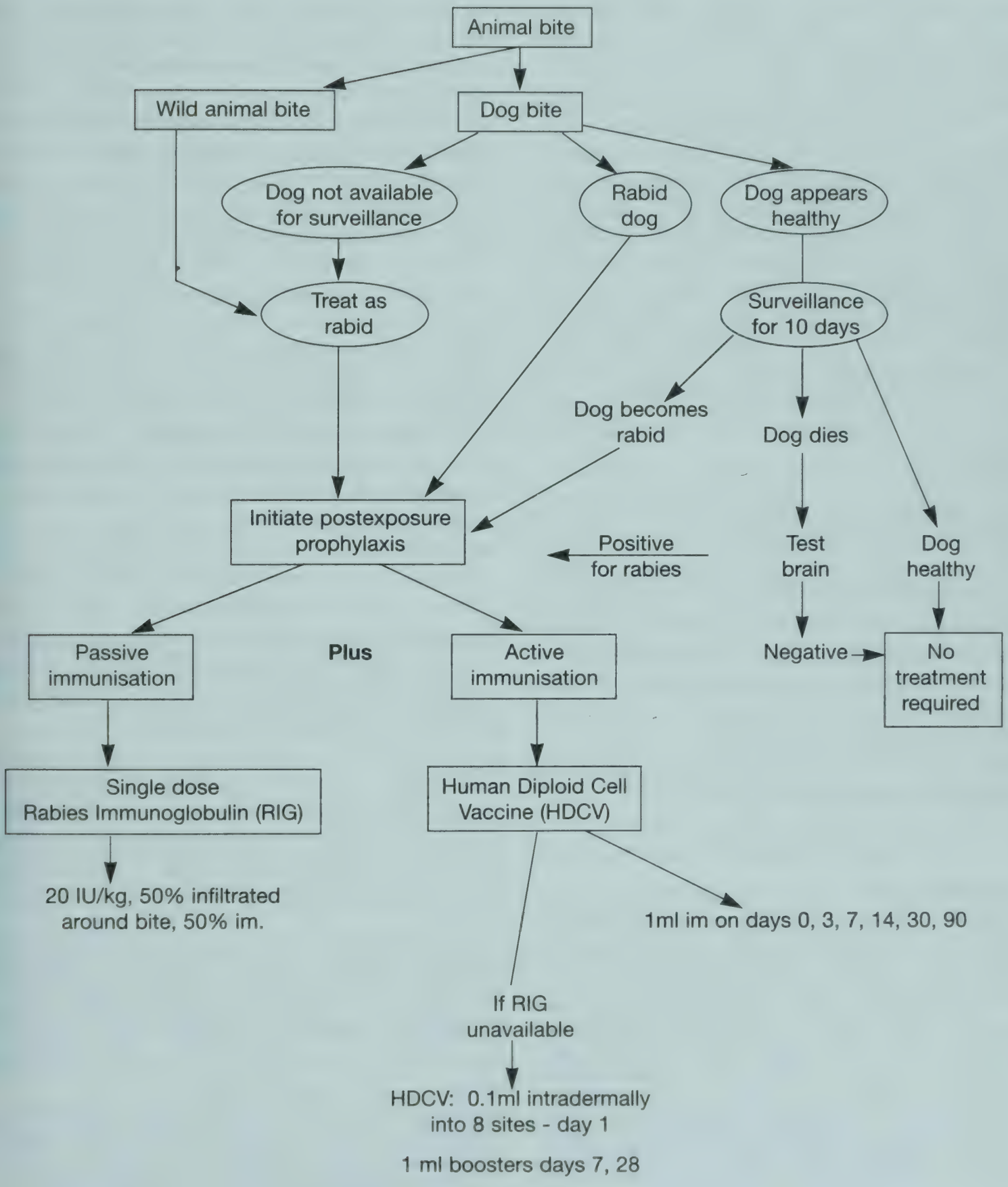
Postexposure prophylaxis: The immediate treatment of a dog bite consists of local wound treatment along with ascertainment of the status of the dog and the immunisation status of the patient.

Local wound treatment consists of washing with a medicinal soap. Deep wounds are flushed thoroughly and mild bleeding is allowed to continue (as blood flow helps to clean the wound). The wound is preferably left unsutured.

Fig 8.15 depicts the further steps in the management of the patient.

Clinical rabies: The treatment of rabies after the onset of disease is symptomatic and consists of supportive care. The patient is isolated in a dark, quiet room. Sedatives (diazepam, as required) and intensive respiratory support are the mainstay of treatment. Nutrition is maintained with intravenous fluids or through a gastrostomy. Though the disease has a very high mortality, a few patients have survived because of excellent supportive care.

Fig 8.15 Postexposure prophylaxis for rabies



Prevention The prevention of rabies consists of impounding stray dogs, vaccination of domestic dogs, and of personnel who handle such animals. Rabies in wild life tends to be self-limiting because of a tendency to eliminate susceptible hosts.

SLOW VIRUS INFECTIONS

Slow virus infections are a group of progressively fatal diseases which primarily affect the central nervous system, have a prolonged incubation phase (from several months to years) and are characterised by the lack of fever or host inflammatory cell response. The diseases included under this definition are: kuru, Creutzfeldt-Jakob disease (CJD), subacute sclerosing panencephalitis (SSPE), and progressive multifocal leukoencephalopathy (PML).[1]

Microbiology Slow viruses may be conventional viruses (papovaviruses which cause PML), defective forms of conventional viruses (such as defective measles virus responsible for SSPE), or unconventional infectious agents (agents causing kuru and CJD). Unconventional agents resemble conventional viruses in being small, and being host-specific but (unlike conventional viruses) contain no nucleic acid (DNA or RNA) and are resistant to inactivation by physical and chemical agents.

Creutzfeldt-Jakob Disease

Etiopathogenesis Creutzfeldt-Jakob disease (CJD)is a potentially transmissible dementia caused by an agent termed a *prion*. Prions are small proteinaceous infectious particles which resist inactivation by procedures which modify nucleic acids. Prion-like proteins are present in the normal host cell. This may explain why no serologic response to prions is generated. It is intriguing, however, that a variant of a normal cellular protein can be the cause of a transmittable disease. For example, PrPC is a membrane sialoglycoprotein in normal human cells, the gene for which has been mapped to chromosome 20. Its function is not entirely known. In individuals with CJD, an abnormal isoform of this protein, PrPSc, aggregates as a constituent of amyloid plaques and fibrils.[2]

Epidemiology CJD is a rare disease with an estimated annual incidence of approximately one per one million persons. Men and women are affected equally. Although the majority of cases is sporadic (a conversion of the normal protein PrPC to the abnormal isoform PrPSc occurs sporadically in these patients), a familial variant has been described. CJD can also be accquired by infection with the PrPSc isoform. Human to human transmission has been reported in association with corneal transplants, and with the use of growth hormone (from pooled human pituitary extracts) in patients with pituitary insufficiency and short stature.

Pathology CJD is a classical example of a spongiform encephalopathy: vacuolated neurons within the grey matter (spongiform changes), astrocytic proliferation and, occasionally, amyloid plaques are seen in the cerebral cortex.

Clinical features and diagnosis CJD is a disorder of late middle age. The disease is characterised by slow onset of dementia associated with myoclonus, and motor dysfunction. Dementia tends to be severe and dominates the clinical course.

[1] The term has now been expanded to include other illnesses which may not meet all these criteria. For instance, chronic viral hepatitis (type B virus, the delta agent, and non-A, non-B virus), cutaneous warts (papillomaviruses), and a number of virus-associated malignant diseases, including Burkitt's lymphoma and nasopharyngeal carcinoma (Epstein-Barr virus), hepatoma (hepatitis B virus), and cervical carcinoma (papillomavirus), are considered by some authorities as slow virus infections.

[2] PrPSc has the same aminoacid sequence as the PrPC; differences in posttranslational events lead to differences in biochemical properties of these two proteins. PrPSc gets deposited as an insoluble amyloid while PrPC is soluble.

The blood biochemistry and CSF profile are normal. The EEG is frequently abnormal showing bursts of high-voltage slow-wave activity. A head CT scan may reveal ventricular enlargement and cerebral atrophy. MRI scans reveal increased signal intensity in the affected areas. CJD rapidly progresses to death, usually over six months. A definitive diagnosis requires a brain biopsy with histopathologic demonstration of the classic spongiform changes. Examination of the biopsy samples under an electron microscope may reveal prion aggregates.

Management There is no effective treatment for CJD. Care should be taken when handling potentially infectious patient material such as the brain, dura or the cornea. The transmittable agent is resistant to boiling, formalin and conventional autoclaving. It is destroyed by immersion in 5 per cent sodium hypochlorite for 1 hour or autoclaving at 132 degrees centigrade (15 lb/in^2) for 1 hour.

Kuru

Epidemiology Kuru,[1] is a slow virus infection, endemic to the Fore tribe in the Papua region of Papua New Guinea, which is acquired through a ritual of cannibalism. The mourning of a dead person in this region was associated with a ritual of eating the brain tissue of the deceased by other family members. The incidence of kuru has declined dramatically with the cessation of this ritual in Papua New Guinea. It has been shown that the same prion protein is deposited as amyloid in kuru, CJD and some slow virus diseases of animals, scrapie in sheep (hence the name PrPSc proteinaceous particle of scrapie) and bovine spongiform encephalopathy in cattle.

Pathology Kuru is characterised by vacuolated neurons within the grey matter (spongiform changes), astrocytic proliferation and occasionally, amyloid plaques. The cerebellum and extrapyramidal tracts are predominantly affected.

Clinical features The disease predominantly affects women and young people who practise the ritual. Kuru is characterised by the progressive onset of cerebellar dysfunction; the affected individual has ataxia, tremor, and dysarthria. Wild athetoid movements occur later and the patient becomes bedridden and incontinent. After 3–6 months, mental faculties deteriorate. The disease is rapidly fatal, with death occurring within one year after the onset of clinical symptoms.

The white blood cell count and CSF are normal.

Treatment There is no known cure for kuru. Treatment is symptomatic. Prevention of the disease requires cessation of the ritual described.

Subacute Sclerosing Panencephalitis

Etiopathogenesis Subacute sclerosing panencephalitis (SSPE) is caused by a defective form of the measles virus. SSPE occurs as a late complication of a measles infection; the virus persists in the brain and lymphoid tissue (including blood lymphocytes) in a modified form. It differs from measles encephalitis which occurs acutely during an attack of measles.

Epidemiology SSPE is a rare disease. It is estimated to occur with an estimated frequency of 1 per 300,000 cases of measles. It is typically seen in individuals who had measles before the age of two years. Men are affected three times more often than women.

Pathology SSPE is characterised by lymphocytic infiltration, nerve cell degeneration, and intranuclear inclusions involving both white and grey matter. Demyelination is a late finding along

[1] Means shivering or trembling in the native language of New Guinea

with fibrous gliosis (hence called 'sclerosing encephalitis').

Clinical features and diagnosis SSPE typically presents as deteriorating intellectual function in a young person (age 5–20 years). With disease progression, periodic myoclonus (a myoclonic jerk occurs predictably every 5–8 seconds in classic SSPE), ataxia, blindness (due to chorioretinitis), seizures, and muscular rigidity develop. SSPE is marked by a gradual downhill course resulting in death within 1 to 3 years.

Markedly elevated levels of measles antibody are present in both the serum and the CSF. EEG findings are also typical; a pattern of burst suppression[1] and biphasic sharp and slow waves is seen. CT and MRI pictures may detect non-specific parenchymal abnormalities. A brain biopsy is not usually required for the diagnosis. If performed, the measles antigen can be demonstrated by immunofluorescence analysis, and the virions can be detected on electron microscopy.

Treatment There is no known treatment for SSPE. Measles vaccination is an important preventive measure.

Progressive Multifocal Leukoencephalopathy (PML)

Etiopathogenesis PML is a progressive demyelinating disease caused by the JC virus.[2] The JC virus is a small, non-enveloped, double-stranded DNA virus belonging to the family Papovaviridae (genus Polyomavirus). Most persons with PML are believed to have been infected with the virus in late childhood. The primary infection is probably acquired by the respiratory route. The virus lies dormant only to undergo reactivation much later, usually in the setting of immunosuppression (organ transplantation, malignant disease, HIV infection). Oligodendrocytes are the target cells for the JC virus.

Epidemiology PML is a rare disease which affects both males and females equally. Typically, PML affects older people. The epidemiology of PML has undergone some change with the rising incidence of AIDS. Since AIDS patients are particularly susceptible to this disease, the incidence of PML in the young adult population has increased.

Pathology PML affects the subcortical cerebral white matter in a multifocal asymmetric fashion. Areas of demyelination, enlarged oligodendrocytes with intranuclear inclusions, enlarged abnormal astrocytes are typically seen. There is a conspicuous absence of any perivascular inflammation.

Clinical features and diagnosis PML usually presents initially as an alteration of mental state and ability. Speech and sensory abnormalities develop soon along with motor paralysis. The patient may develop cortical blindness. The disease progresses inexorably to death within six months.

The CSF profile is normal. The EEG may show non-specific abnormalities. A head CT scan reveals multifocal hypodense areas in the cerebral white matter.

An MRI scan may be obtained if available as it is particularly sensitive in detecting lesions in the white matter.

A definitive diagnosis requires histopathologic examination of the brain tissue. JC viral antigen is detected by immunofluorescence techniques, and electron microscopy reveals dense arrays of virions.

Treatment There is no known treatment for PML.

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[1] Each myoclonic jerk is preceded by a 'burst'.

[2] The name is derived from the initials of the patient from whom the virus was originally isolated.

KEY CONCEPTS

Influenza

- Three enveloped myxoviruses (A,B,C) can cause the illness; variation of the surface glycoproteins results in new strains permitting pandemics to occur in non-immune populations
- Infection is transmitted by droplets. Respiratory tract infection is typical and individuals at extremes of age are at increased risk. The peak incidence is in winter and in patients with COPD.
- Influenza manifests as an acute illness characterised by coryza, severe myalgia, prostration, and cough. *Complications* include viral pneumonia (second week) or superimposed bacterial pneumonia (recovery phase). Children treated with aspirin are at risk of developing Reye syndrome.
- The diagnosis is clinical; the absence of tonsillar exudate and the marked systemic symptoms distinguish influenza from bacterial pharyngitis and from a common cold, respectively. The epidemiologic setting is suggestive.
- Treatment is mainly with supportive care. Amantadine has a beneficial effect on the fever and respiratory symptoms if started early, and if the infection is due to Type A virus.

Herpes simplex

- Two viruses are recognised: *Type I* (affects children; lesions *above waist*) and *Type II* (affects adults; lesions *below waist*). Herpes is transmitted by contact with infected skin, secretions or mucosa.
- Initial infections are often asymptomatic. The virus lies latent in sensory ganglia and *reactivates* with triggers (menses, stress or decreased immunity). Recurrences tend to be painful.
- HSV I causes a spectrum of illness: *gingivostomatitis,* herpes *labialis,* punctate *keratitis,* herpetic *whitlow.* The typical lesion is a vesicle on an erythematous base.
- *Herpes encephalitis* is most often due to Type I; it is the most common sporadic viral encephalitis. Onset of the disease is with fever and encephalopathy. The presence of seizures and focal findings localisable to the temporal or frontal lobes are highly suggestive.
- HSV II often causes genital vesicles, ulcers and pruritus. It may also cause proctitis and autonomic dysfunction.
- Diagnosis is possible if multinucleate giant cells are seen in a Giemsa-stained smear from the base of the mucocutaneous lesion (*Tzanck smear*). HSV encephalitis is suggested by characteristic EEG findings; CSF shows lymphocytosis; definitive diagnosis requires positive PCR in CSF or brain biopsy. An MRI may be helpful.
- Treatment is with topical/oral acyclovir for superficial lesions; i.v. for HSV encephalitis. Vidarabine/idoxuridine may be used for eye infections.

AIDS

- Infection caused by HIV-I and 2 which is associated with immune dysfunction and a typical clinical syndrome
- Transmitted by sexual contact (homosexuals at high risk; commercial sex workers are a reservoir in tropics), i.v. drug abuse, transfusions (hemophiliacs at high risk) or by transplacental mode
- Four groups of HIV infection are recognised: 1) *initial* infection (characterised by fever, arthralgia); 2) *asymptomatic infection* with *evidence of immune and hematologic dysfunction;* 3) *persistent generalised lymphadenopathy* with laboratory features as above; 4) full blown *AIDS* defined by: constitutional symptoms; neurologic symptoms (dementia, painful sensory neuropathy); disseminated zoster/herpes simplex/CMV; Pneumocystis carinii pneumonia; secondary cancers such as Kaposi's sarcoma, primary CNS lymphoma; low CD_4 count (<200/mm^3)
- Diagnosis of HIV infection can be confirmed by detection of anti-HIV antibody. If ELISA is positive, it is repeated; if it positive again, confirm with Western blot.

  Routine investigations should include CD_4/CD_8 ratio in peripheral blood, blood cultures, chest X-ray.
- Treatment is with AZT+DDI; pentamidine is initiated for prophylaxis of Pneumocystis infection if CD_4 count is <200/mm^3; treat opportunistic infections aggressively.

Arboviruses

Dengue fever

- Dengue is a flavivirus that can cause *dengue fever* and *dengue hemorrhagic fever* (DHF); the vector is the *Aedes* mosquito
- *Dengue fever* mainly affects adults and is characterised by high fever (*saddleback pattern*), severe myalgia, arthralgia, backache and headache. Rash and lymphadenopathy may be present.
- *DHF* occurs more often in children. Unlike dengue fever, respiratory and GI symptoms are prominent (myalgia may be absent). The hallmark is petechial rash, bleeding tendency and shock.
- Leucopenia is common in dengue fever; DHF is characterised by hemoconcentration and thrombocytopenia.

- The treatment is symptomatic; avoid aspirin as an antipyretic. DHF may require fresh blood/platelet transfusions.

Japanese encephalitis

- This is a flavivirus infection endemic in southeast Asia; *Culex vishnui complex* mosquitoes are the vectors.
- Asymptomatic infections outnumber symptomatic ones (30:1). The symptoms include headache, encephalitis, meningitis and seizures. Focal reversible neurologic deficits are frequent.
- The diagnosis is by serology.
- The treatment is supportive; the disease has a high fatality (20–40%).

Rabies

- Rabies is a lethal encephalitis resulting from the bite of an infected dog or wild animal.
- The disease has a long incubation period (3–15 weeks). The virus results in increased reflex activity of brain stem neurons. Illness manifests as hypersalivation, disorientation, seizures, spasms of laryngeal and pharyngeal musculature (often provoked by the sight of water), and progressive deterioration leading to coma and death.
- The brain of the affected rabid dog may demonstrate *Negri bodies*. The diagnosis is by examination of the corneal scraping obtained from the patient or by brain biopsy.
- No specific treatment other than supportive care (respiratory, circulatory care) is known; the disease has a very high fatality. Proper nursing precautions need to be followed as the saliva and secretions contain the infective virus. If the animal is suspected to be rabid, the patient is treated with rabies immunoglobulin and HDCV (vaccine; 6 i.m. injections) simultaneously.
- Prevention is by immunisation of domestic pets and control of wild animals, and vaccination of workers at a high risk.

Prion and slow virus infections

Creutzfeldt-Jakob disease

- This is a *subacute spongiform encephalopathy* due to an infectious *prion* particle; it may be sporadic, or may be acquired by handling infected tissues or during corneal transplantation.
- Its cardinal features are the onset of a progressive dementia with prominent myoclonic seizures in a middle-aged adult.
- The EEG is suggestive but a brain biopsy may be required for definitive diagnosis.
- No treatment is known and the disease is rapidly fatal over months.

Subacute sclerosing panencephalitis

- It is progressive with fatal neurologic illness occurring years after an episode of measles (usually before the age of 2 years).
- The patient is typically a child or an adolescent who manifests progressive cognitive decline along with myoclonic seizures. Focal chorioretinitis with maculopathy seen in some patients.
- The EEG shows bursts with slowing of background activity. The CSF shows elevated γ-globulins and a low serum/CSF anti-measles IgG ratio.
- No treatment (isoprinosine may slow the rate) is available and the disease is fatal within 1–3 years.

Progressive multifocal leucoencephalopathy

- This is a papova virus (JC) infection principally affecting immunocompromised individuals (leukemia, lymphoma).
- The clinical features consist of progressive intellectual deterioration, ataxia, visual disturbances, cortical blindness and brainstem signs.
- White matter lesions are evident on a CT/MRI.
- No effective treatment is available; the disease is rapidly fatal in less than 6 months.

8.8 Diseases due to Rickettsiae, Mycoplasma and Chlamydiae

RICKETTSIAE

Epidemiology Rickettsiae are obligate intracellular organisms resembling viruses and bacteria. They are seen microscopically as pleomorphic coccobacilli which stain purple with Giemsa. Most rickettsiae are maintained in nature by a cycle involving an animal reservoir and an arthropod vector which infects humans. Humans are accidental hosts when they are exposed to the arthropod vector. Q fever is not transmitted by an arthropod; inhalation of infected aerosol or ingestion of infected milk is the method of transmission.

Clinical features Rickettsiae belonging to the typhus or spotted fever group (Table 8.28) infect humans through the bite of a louse, mite, tick or flea. The rickettsiae multiply at the site of inoculation and in some cases produce a local lesion called an *eschar*. The rickettsiae then penetrate the skin and multiply within the endothelial cells of small blood vessels. The result is a vasculitis consisting of endothelial cell proliferation, perivascular infiltration and thrombosis. The *endovasculitis* accounts for most of the clinical manifestations including rash, encephalitis and gangrene of the skin and other tissues. Fever is a prominent part of the illness. Q fever is an exception in that there is no rash and the predominant presentation is as an atypical pneumonia.

Diagnosis During convalescence from rickettsial illness, patients have agglutinins against specific *Proteus* strains in their serum—the Weil-Felix reaction (against antigens OX-19, 2 and K). Species-specific antibodies may also be detected by complement fixation tests.

Management Rickettsial fevers respond to tetracycline (25 mg/kg divided into 3 to 4 doses) or chloramphenicol (50 mg/kg in divided doses). Supportive measures include antipyretics (for fever), sedatives (for delirium) and blood transfusions (for hemorrhage).

MYCOPLASMA

Microbiology Mycoplasma are the smallest known free-living organisms. Unlike bacteria, mycoplasma lack a rigid cell wall and do not synthesise folic acid. Consequently, all mycoplasma are resistant to antibiotics such as the penicillins, cephalosporins (whose site of action is the bacterial cell wall), and sulfonamides (which block folic acid synthesis). They are, however, susceptible to the macrolides and tetracyclines. Only three species, M. pneumoniae, M. hominis, and U. urealyticum are pathogenic for humans. Ureaplasma are distinguished from Mycoplasma species by their ability to metabolise urea. Mycoplasma can be cultivated on solid culture medium (broth or agar supplemented with yeast extract and 20 per cent horse serum) where the colonies of most species exhibit a *fried egg* appearance[1].

[1] The central portion of the colony penetrates deep into the agar and is surrounded by secondary superficial growth.

Table 8.28 Diseases due to Rickettsiae

Disease	*Etiology*	*Epidemiology*	*Symptoms*			*Diagnosis Weil-Felix test*
			eschar	*distribution*	*rash*	
Typhus group						
1. Epidemic typhus	R. prowazekii	bite of body louse	none	Trunk → extremities	morbilliform	positive OX-19
2. Endemic (murine) typhus	R. typhi	bite of rat flea	none	Trunk → extremities	macular	positive OX-19
3. Scrub typhus	R. tsuttsugamushi	bite of trombiculid mite	present	Trunk → extremities	maculo-papular	positive OX-K
Spotted fever group						
1. Rocky Mountain Spotted fever	R. rickettsii	bite of tick	none	Extremities → trunk, face	maculo-papular, petechial	positive OX-19 and OX-2
2. Ricketssial pox	R. akari	bite of mite	present	Trunk → face, extremities →	papulo-vesicular	negative
3. Boutonneuse fever	R. conori	dog tick	present	Trunk, extremities, face, palms	maculo-papular, petechial	—
Other rickettsial diseases						
1. Q fever	Coxiella burnetii	aerosol of infected materials or infected milk	none, dominant feature is pneumonia	none	—	negative, diagnosis by serology
2. Trench fever	Rochalimaea quintana	bite of body louse	none	trunk	macular	negative

M. pneumoniae colonies do not exhibit the typical fried egg pattern but rather have a more homogeneous appearance. Ureaplasma species produce tiny colonies on solid medium.[1]

M. Pneumoniae Infections

M. pneumoniae infection can also manifest clinically as a pneumonia, as tracheobronchitis, or as pharyngitis.

Epidemiology Mycoplasma pneumoniae is endemic in crowded urban areas; it is one of the most common causes of pneumonia in the community. Children between 5 and 15 years of age are most commonly infected. M. pneumoniae is transmitted by infected droplets of respiratory secretions. The spread of Mycoplasma pneumonia from one person to another usually requires close and prolonged contact. The disease has an incubation period of two to four weeks and characteristically spreads slowly within a family.

Pathogenesis M. pneumoniae organisms penetrate mucociliary secretions and adhere to the surface of respiratory epithelial cells where they multiply extracellularly and cause local mucosal damage and ciliary stasis without actually invading the mucosal cells. M. pneumoniae alters the erythrocyte I antigen rendering it immunogenic; this results in the development of complement-fixing, temperature-sensitive IgM antibodies directed against this erythrocyte membrane protein. This accounts for the presence of a positive direct Coombs' test in over 80 per cent of patients with M. pneumoniae infection; clinically significant hemolysis is rare.

Clinical features About a fifth of M. pneumoniae infections are asymptomatic. Tracheobronchitis or an upper respiratory syndrome characterised by pharyngitis, fever, and headache is more common than pneumonia, which occurs in 5–15 per cent of infected cases. A non-productive cough is the most common presenting symptom of M. pneumoniae pneumonitis. Headache, malaise, chills, and a fever of 38–40°C are present frequently. The onset is subacute in most patients. Although fine to medium pulmonary rales can be auscultated in most patients with M. pneumonia bronchial breath sounds (the clinical hallmark of a consolidation) are noted less frequently. Many patients have severe symptoms but scant physical findings; pneumonia can be diagnosed only with a chest X-ray. The illness is self-limited, having a course of one to three weeks. Two helpful features in the diagnosis of M. pneumoniae infection are inflammation of the tympanic membrane and a skin rash; bullous myringitis may be noted in about 25 per cent of cases and erythema multiforme is the most important associated skin eruption. Neurologic involvement may be present in less than 5 per cent of patients and includes a spectrum of findings: meningoencephalitis, encephalitis, a Guillain-Barre-like syndrome, cerebellar ataxia and aseptic meningitis.

Diagnostic investigations Laboratory diagnosis of an M. pneumoniae infection in a patient with primary atypical pneumonia is established by 1) the finding of a rising (or already high) titre of cold agglutinins, and 2) the results of specific serologic tests (such as the complement fixation test). The peripheral leukocyte count is normal in most patients with M. pneumonia. About 50 to 60 per cent of patients with M. pneumoniae pneumonia show a fourfold or greater rise in the cold agglutinin titre for human type O erythrocytes or have a single titre of 1:128 or higher.[2] Sputum smears from patients with

That is why they were originally called T strains or T mycoplasmas

[2] The physician can screen for the presence of cold agglutinins by means of a simple bedside test: four to five drops of blood are added to a test tube containing sodium citrate; the tube is immersed in ice-cold water for 30 seconds and then tilted so that the blood runs down the side. Definite flocculation which disappears after the tube is incubated at 37 °C indicates a positive reaction. This screening test correlates well with cold agglutinin titres of 1:64 or greater. Low titres (<1:32) may occur with infectious mononucleosis and with pneumonias caused by adenovirus or influenza virus.

M. pneumonia generally reveal large mononuclear cells and some granulocytes. Radiologic abnormalities of primary atypical pneumonias of all etiologies are similar. Patchy alveolar infiltrates that involve one of the lower lobes are typical. Pleural involvement is rare. Radiologic abnormalities may persist for upto 4 weeks or more. Since none of the above tests is likely to provide positive confirmation of the diagnosis early in the illness, therapy is often initiated based on clinical and radiologic findings alone. Bacterial pneumonia should be ruled out on the basis of the peripheral leukocyte count, Gram-stain of the sputum, and sputum culture. The other causes of primary atypical pneumonias that should be considered in the differential diagnosis include infections with psittacosis, C. pneumoniae, Q fever, tularemia, and viral pneumonias (due to adenoviruses, influenza or parainfluenza, or respiratory syncytial virus).

Treatment Erythromycin (250–500 mg four times daily for 10–14 days) or a tetracycline (250–500 mg four times daily) is the antibiotic of choice in the treatment of M. pneumoniae pneumonia. Erythromycin is preferable in children because it does not stain the teeth.

CHLAMYDIAE

Trachoma

Trachoma is a chronic follicular conjunctivitis due to *Chlamydia trachomatis,* usually serotypes A, B, Ba, or C.

Epidemiology There are about 500 million people worldwide affected by trachoma and of these 5–10 million people are blind. Trachoma is directly or indirectly responsible for approximately a quarter of the blindness in the world. Trachoma predominantly affects young preschool children; repeated episodes of infection and prolonged bouts of intense inflammation can eventually lead to blindness. Women who are in prolonged contact with infected children are three times more at risk of developing blindness from trachoma.

Clinical features Trachoma begins as a mild infection, resembling bacterial conjunctivitis which is associated with conjunctival congestion, lacrimation, photophobia and eyelid edema. If left untreated, over the course of the next month, small conjunctival follicles develop in the conjunctiva of the upper eyelid. These yellow-grey 'sago-grain' granulations are surrounded by inflammatory papillae. Soon small blood vessels invade the upper half of the cornea from the limbus; this tissue is called 'pannus'. Eventually the stage of cicatrisation sets in, with inturning of the eyelids (entropion). The eyelashes rub against the cornea (trichiasis). The corneal epithelium gets dull and thickened. Ulcers may form on the cornea and secondary bacterial infection is common. Obstruction of the lacrimal glands may result in dry eyes. The WHO grading of trachoma infection is listed in Table 8.29.

Diagnosis Trachoma is readily diagnosed by the demonstration of characteristic inclusions which are seen within the epithelial cells with a Giemsa stain or with direct fluorescent antibody cytology of conjunctival scrapings.

Treatment Trachoma has been traditionally treated with 1% tetracycline ointment used 2 to 4 times a day for 1–3 weeks, and possibly repeated upto 6 times at monthly intervals. Topical therapy is relatively ineffective, although it has been recommended by the WHO. Oral tetracyclines, doxycycline, sulfonamides and cotrimoxazole are effective alternatives.

Prevention Recent studies have emphasised that simple measures aimed at ensuring personal hygiene and facial cleanliness can dramatically impact trachoma infection by breaking the cycles of repeated episodes of infection; only 100 ml of water is needed to wash a child's face. The shared use of 'surma' in north India among children within a family is another preventable mode of transmission.

Table 8.29 World Health Organization simplified trachoma grading scheme

TF	Trachomatous inflammation—follicular; 5 or more follicles (≥0.5 mm) in the upper tarsal conjunctiva
TI	Trachomatous inflammation—intense; inflammatory thickening of tarsal conjunctiva obscuring more than half of the normal deep tarsal vessels
TS	Trachomatous conjunctival scarring; easily visible scarring in the tarsal conjunctiva
TT	Trachomatous trichiasis; at least one eyelash rubbing on the eyeball
CO	Corneal opacity; easily visible opacity over the pupil obscuring at least part of the pupil margin

Lymphogranuloma venereum caused by a ype of chlamydia trachomatis has been iscussed earlier under sexually transmitted iseases.

Psittacosis

sittacosis is an acute febrile infection of humans aused by *Chlamydia psittaci.* The disease is haracterised primarily by a pneumonia with rominent systemic manifestations. It is ansmitted to humans by a variety of psittacine irds (parrots and parakeets).[1]

pidemiology and pathogenesis Psittacosis is n occupational disease of poultry workers. ncidence is also reported among owners of pet irds. Psittacosis is transmitted from infected irds when human beings inhale dust from the eathers or bird droppings. *C. psittaci* enters the uman body through the respiratory tract. The rganism rapidly disseminates from the lungs to ne reticuloendothelial system through the loodstream. The major sites of localisation of ne organism are the lungs, the liver and the pleen.

linical features The incubation period ranges om 1–3 weeks. Psittacosis varies in severity om a mild influenza-like illness to a severe neumonia. High fever (39–41°C) is prominent uring the first week of illness. A hacking, on-productive cough, severe headache and prominent gastrointestinal symptoms are clues to the possibility of psittacosis in a person with pneumonia; relative bradycardia and splenomegaly (10%) are additional important clues on physical examination. Lung findings on clinical examination are less prominent than would be expected on the basis of the radiologic changes (clinical-roentgenographic discrepancy). The liver may be enlarged and palpable. Rarely, a rash (Horder's spots) resembling the rose spots of typhoid fever, may appear. Neurological symptoms have also been described and are attributed to a mild meningoencephalitis. Clinical recovery usually occurs in 7 to 10 days.

Differential diagnosis A history of contact with birds provides an important clue to the diagnosis of psittacosis in a patient with pneumonia, especially if bradycardia and splenomegaly are also present. Differentiation of psittacosis from influenza, viral pneumonia and other atypical pneumonia solely on clinical grounds may be difficult. Definitive diagnosis requires demonstration of a significant antibody rise or isolation of the etiologic agent.

Investigations The total blood leukocyte count is usually normal. The chest X-ray reveals a patchy bronchopneumonia; hilar prominence may be present. Abnormalities of liver function tests may be evident; serum levels of aspartate aminotransferase, alkaline phosphatase, and bilirubin may be elevated. The organism can be isolated from the sputum and blood of patients

[1] The same disease is called ornithosis when it is acquired from non-psittacine birds (pigeons, chickens, pheasants, and turkeys).

during the first two weeks of illness. Laboratory diagnosis can also be made by demonstrating a fourfold or greater rise in complement-fixing or fluorescent antibody titre to a group antigen.

Treatment Tetracycline (0.5 g orally every six hours) or doxycycline (0.1 g orally twice daily) is the treatment of choice. Treatment should be continued for seven to 10 days after defervescence. Clearing of the pulmonary lesion on X-ray can take upto six weeks.

Chlamydia Pneumoniae Infections

Epidemiology Humans are the only known natural hosts for *C. pneumoniae.*[1] C. pneumoniae infections are endemic worldwide; superimposed epidemic periods occur every three to four years. Person to person transmission occurs principally by the aerosol route.

Clinical features The majority of C. pneumoniae infections are asymptomatic; serologic evidence of exposure is present in a majority of adults. Pneumonia, bronchitis and pharyngitis are the most common clinical syndromes caused by C. pneumoniae. The symptoms of lung infection resemble those of other atypical pneumonias. Hoarseness of the voice is, however, more common in C. pneumoniae infection. C. pneumoniae has also been reported to cause endocarditis, myocarditis, hepatitis, aseptic meningitis, and an erythema nodosum-like syndrome.

Investigations The peripheral blood whitecell count is usually withing normal limits but the erythrocyte sedimentation rate is often elevated. Chest radiographs most often demonstrate a unilateral lower lobe subsegmental infiltrate with an interstitial pattern. A specific laboratory diagnosis must be based on serologic tests or culture. The preferred serologic diagnostic method is microimmunofluorescence,[2] a technique that is available only in reference laboratories.

Treatment Tetracycline (0.5 g orally every six hours), doxycycline (0.1 g orally twice daily), and erythromycin (0.5 g orally every six hours) administered for two to three weeks have all been shown to be effective against C. pneumoniae infection.

[1] Also initially called the TWAR strain after the original two isolates, TW-183 isolated in Taiwan and AR-39 isolated in Seattle, USA

[2] Microimmunofluorescence detects species-specific antibodies directed against chlamydial outer membrane proteins.

KEY CONCEPTS

Rickettsial diseases

- There are due to obligate intracellular organisms is injected by the bite of the arthropod vector; local eschar is followed by the proliferation of organisms within the endothelial cells. The resultant vasculitis results in a rash, encephalitic signs, and digital gangrene. The nature of the vector (louse, flea, mite) and the type of rash varies with individual species.
- Positive serum agglutinins to the *Proteus* species are seen.
- Q fever is transmitted by aerosol (not by a vector), manifests as pneumonitis and rash is absent.
- Chloramphenicol or tetracycline are the drugs of choice.

Mycoplasma pneumoniae

- This disease affects young adults most often. Respiratory infection is the most common mani-festation: *tracheobronchitis,* with mild nonproductive cough, headache. It is the most common cause of community-acquired *pneumonia.* Associated features include *erythema multiforme* and *bullous myringitis.*
- Elevation of IgM cold agglutinins is suggestive; a four-fold rise in Ab titre is diagnostic.
- Treatment is with erythromycin/tetracycline.

Trachoma

- This is a chronic granulomatous conjunctivitis which is transmitted by hand to eye contact or shared contaminated articles (such as surma). It is endemic in the tropics.
- Conjunctival follicular hypertrophy results in *sago grain* granulations, *pannus* formation, and the resultant vascularisation of the cornea with consequent development of corneal opacities.
- Basophilic inclusion bodies on a Giemsa stain of conjunctival scraping are diagnostic.
- Tetracycline (oral + topical) or oral cotrimoxazole is effective.

8.9 Protozoal infections

MALARIA

Malaria is one of the most important parasitic infections of humans; it is caused by the protozoan *Plasmodium* species and the *Anopheles* mosquito is the vector.

Epidemiology It is currently estimated that there are about 300 million people afflicted with malaria globally at any point of time and the annual death toll is 1–2.5 million. Different species predominate in different regions of the word: P. vivax is the commonest form in India whereas P. falciparum is the commonest form in Africa. Malarial transmission varies from country to country depending on a variety of factors such as altitude, temperature and rainfall. Evening and night time exposure is associated with a greater risk as it corresponds with the feeding time of the Anopheles species.

Clinical microbiology The four species of Plasmodium that infect humans are, in order of decreasing worldwide prevalence, *P. falciparum, P. vivax, P. malariae* and *P. ovale.* Plasmodia primarily infect the host erythrocytes. The intraerythrocytic form of the four species is distinctive, permitting species identification.

Malarial infection is initiated by the bite of an infected female Anopheles mosquito. During its blood meal, the mosquito injects sporozoites into the host blood. These sporozoites circulate in the capillaries for less than 30 minutes before entering the liver where the hepatic *exo-erythrocytic* stage takes place. A single parasite produces tens of thousands of *merozoites* that eventually rupture the liver cell releasing the merozoites into circulation. The *erythrocytic* phase then commences with the parasites invading the red blood cells. Inside the erythrocytes, the parasites begin to feed on hemoglobin and then divide asexually by a process called *schizogony.* The parasites develop from the ring stage to mature trophozoites which in turn develop into *schizonts.* The merozoites arising from this process rupture out of the infected erythrocyte and invade other adjacent erythrocytes. Sexual differentiation of the intraerythrocytic parasite results in *gametocytes* that can be taken up by the mosquito fertilisation in the gut wall of the mosquito results in zygote formation and production of the infective forms—the sporozoites.

Certain peculiarities of individual Plasmodium species dictate the clinical manifestations. In the case of *P. vivax* and *P. ovale,* some of the exo-erythrocytic forms remain latent in the liver cells as *hypnozoites* and these can mediate relapses. P. malariae is unique in that it can persist in circulation at undetectable levels for years; it is associated with blood tranfusion associated malaria. The successful attachment of *P. vivax* to the red cell requires the presence of *Duffy a* and determinants on the erythrocyte membrane. Because most Africans are *Duffy* negative *P. vivax* infection is uncommon in this part of the world. Similar impediments to red cell invasion

re the presence of *glucose-6 phosphate ehydrogenase* deficiency and an abnormal emoglobin such as *Hb S* (sickle cell). These alaria-resistant traits are more prevalent in frica due to the natural selection of these dividuals. The age of the red cell is an dditional factor which influences the sceptibility to infection. *P. vivax* and *P. ovale* fect only young erythrocytes, whereas *malariae* infects only mature cells. Because inical severity is related to the degree of arasitemia, infections due to these three species ldom, if ever, lead to fatality. *P. falciparum,* in ntrast, can invade erythrocytes of any age; this n lead to massive parasitemia and severe sease. *P. falciparum* also induces the pression of an adhesive protein on the surface the red cells (electron-dense excrescences lled knobs), which leads to cytoadherence of e infected cells to the vascular endothelium. his process is known as sequestration and can ad to microcirculatory obstruction and sturbance of the function of vital organs.

The time for intracellular development of erozoites is important as it determines the eriodicity of febrile paroxysms (see below); it is 2 hours for *P. malariae* and 48 hours for the maining three species. If schizogony is nchronised (that is, all infected red cells arbour parasites at the same stage of evelopment), fever spikes occur every 72 hours *P. malariae* (hence the term *quartan malaria*) nd every 48 hours in the others (*tertian alaria*).

linical features The clinical features of alaria are related to the consequences of the pture of erythrocytes and release of erozoites. Periodic fever spikes are the stinguishing feature of malaria. These febrile aroxysms are preceded by a prodromal period 1–2 days characterised by low-grade fever, alaise, myalgia and headache. This flu-like ness may be associated with upper respiratory act symptoms such as cough and may be isleading. The febrile paroxysm has typically three phases. The initial cold phase begins and is characterised by temperature elevations of upto 102–104°F. The skin is hot and dry and there may be headache. The hot stage is followed by a phase of defervescence when the temperature returns to normal. This phase is characterised by diaphoresis and exhaustion. Paroxysms return in 48–72 hours if infection is synchronised (see above).

If untreated, the cycles of infection are associated with clinical anemia and splenomegaly, and hepatomegaly may be detected. Tachycardia, tachypnea and hypotension are common concomitants of untreated malarial infection.

Complications *P. falciparum* infection is associated with a severe degree of parasitemia and a clinical picture of 'malignant tertian malaria' (as opposed to the 'benign tertian' infection due to P. vivax). The development of unconsciousness is an ominous sign and signifies 'cerebral' malaria. The primary mechanism seems to be sequestration of parasites within the cerebral capillaries and venules; cerebral edema and capillary sludging are believed to play a minor role. The progression to coma is often gradual and there may be periods of confusion, delirium and obtundation which precede the illness and herald the final phase. Seizures are common in children and may be associated with aspiration. The clinical signs are those of a symmetrical encephalopathy. There is no evidence of meningeal irritation. Focal neurologic signs are unusual. Pupillary responses and corneal reflexes are usually preserved. Plantar responses may be extensor in upto 50 per cent of cases. Fundoscopy may reveal retinal hemorrhages but papilledema is rare. There may be increases in muscle tone, and extensor posturing is common. Fixed closure of the jaws is common (making intubation difficult) and tooth grinding is also frequent; a jaw jerk is present in a third of patients. Evidence of autonomic involvement is unusual, apart from the frequent presence of postural hypotension.

The level of coma may fluctuate. The usual duration of coma varies from 24 to 48 hours. Recovery is complete if treatment is instituted.

Cerebral malaria is often accompanied by coexistent renal failure and liver impairment with jaundice. Acute renal failure is a major cause of death from P. falciparum infection in the tropics. It results from acute tubular necrosis and may be related to multiple factors which include hypotension, intravascular hemolysis with hemoglobinuria (so-called *blackwater fever*), and disseminated intravascular coagulation.

Lactic acidosis and hypoglycemia are other important complications and carry a poor prognosis. Acute pulmonary edema has been described and appears to be related to increased capillary permeability. Supervening secondary bacterial infection is also a frequent complication of cerebral malaria; some patients develop spontaneous gram-negative septicemia.

Diagnosis The only practical means of establishing a diagnosis of malaria is to demonstrate the presence of intraerythrocytic parasites in smears of the peripheral blood (stained with Giemsa). Blood smears must be obtained on multiple occasions over a 72-hour period to rule out a diagnosis of malaria. If infection is synchronised, smears may be timed a half hour prior to the expected fever spikes. Thick blood smears enable the detection of parasites but thin smears are required for species identification. Thick smears also enable a quantification of the extent of parasitemia; the number of parasites per leukocyte nucleus can be counted and by relating this to the total leukocyte count, the number of parasites per cubic millimetre can be estimated. This is of therapeutic importance (see below).

Other blood tests may be abnormal too. There may be mild anemia, thrombocytopenia, hyponatremia, hyperbilirubinemia and mildly elevated levels of serum transaminases.

Treatment

General principles:

1. There must be a high index of suspicion of malaria as the initial symptoms can be non-specific and misleading. This is important as malaria is endemic in India.
2. Identification of the parasite species is important as P. falciparum infection is treated as a medical emergency due to its potentially fatal complications.
3. The choice of drug treatment regimen is based on the knowledge of the prevalent patterns of drug resistance.
4. Parasitological and clinical response to treatment must be monitored to diagnose treatment failure early.
5. Complications of P. falciparum infection can occur even after the initiation of therapy and the patient is monitored for this potential.

Treatment of uncomplicated infections due to species other than P. falciparum: Chloroquine is the treatment of choice and the standard regimen is 25 mg base/kg; this is conventionally divided into an initial dose of 10 mg/kg, followed by three subsequent doses of 5 mg/kg at 6–12 hour intervals. Defervescence of fever and abatement of symptoms can be expected within 72 hours of starting therapy. Ideally, in infections due to P. vivax and P. ovale, this regimen must be followed up by treatment to eliminate the hepatic hypnozoites which are a potential source of relapses and which are not affected by chloroquine. Primaquine (15 mg/ 22.5 mg daily for 14 days) is the drug of choice for this purpose. Primaquine is a potent oxidant however, and can cause severe hemolysis in patients with deficiency of the enzyme *glucose-6-phosphate dehydrogenase.* Patients should be screened for this enzyme deficiency prior to the institution of primaquine therapy. In patients with this enzyme deficiency, a lower dose (45 mg weekly for 6 weeks) is administered, with careful monitoring for incipient hemolysis.

In chloroquine-resistant areas, a sulfadoxine pyrimethamine combination (1 mg/50mg/kg in

ingle dose)[1] may be used. Mefloquine in a dose of 15–25 mg base/kg[2] is a single dose alternative; he risks of vomiting may be reduced by splitting he higher dose into an initial dose of 15 mg/kg ollowed by another dose of 10 mg/kg after 8 hours. Mefloquine is associated with nausea, dizziness and dysphoria.

If mefloquine resistance is also present in the rea, a supervised course of oral quinine 10 mg alt/kg three times daily plus either tetracycline 4 mg/kg four times a day) or doxycycline 1.5 mg/kg once daily) for seven days may be sed in adults. Quinine is not tolerated well and roduces a symptom complex termed inchonism; tinnitus, dysphoria, deafness and a itter taste are features of this state. Two other lternatives are artesunate[3] (200 mg initial dose ollowed by 100 mg daily for 4 days) and alofantrine (8 mg/kg for three doses[4]). Halofantrine has been associated with diarrhea nd 'electrocardiographic changes' (QT rolongation).

Treatment of complicated infections due to pecies other than P. falciparum : If the patient is very sick or is unable to tolerate oral chloroquine and chloroquine resistance is not present n the area, chloroquine may be adminstered as a slow intravenous infusion (10 mg base/kg over 8 hours followed by 15 mg base/kg over 24 hours) or by intramuscular injection (2.5 mg base/kg every 4 hours). Oral treatment is commenced once the patient is able to swallow. Hypotension and convulsions are notable side effects of parenteral chloroquine therapy.

If chloroquine resistance is known, quinine is the drug of choice and should be administered as indicated in the next section. Other alternatives which are not available easily include artemether (3.2 mg/kg intramuscular followed by 1.6 mg/kg i.m. every 12 hours) or artesunate (2 mg/kg i.v. or i.m. followed by 1 mg/kg every 12 hours). Both drugs are tolerated well.

Treatment of P. falciparum infections: Quinine is the treatment of choice for P. falciparum infections. In the conscious patient, oral quinine sulfate (650 mg tid for 3 days) followed by tetracycline (250 mg qid for 7 days), or pyrimethamine-sulfadoxine (3 tablets single dose) are effective therapeutic regimens.

Severe falciparum malaria is a medical emergency. The patient should be admitted to an intensive care unit if possible. Intravenous lines should be established, and baseline blood samples taken for hematological and biochemical evaluation. Along with institution of treatment, a careful history is obtained about the nature and doses of antimalarials administered and the occurrence of convulsions. The initial clinical assessment should focus on the level of consciousness, adequacy of ventilation, the circulatory state and urinary output. A lumbar puncture should be performed in the unconscious patient. If there is hyper- or hypoventilation, arterial blood gas analysis must be obtained. Intravenous adminstration of quinine is preferable for severe falciparum infections. Quinine hydrochloride is administered intravenously as a loading dose of 20 mg salt/kg infused over 4 hours, followed by 10 mg/kg at 8 hour intervals infused over 2–8 hours.[5] In a rural health facility, quinine may be administered by the intramuscular route (20 mg salt/kg followed by 10 mg/kg every 8–12 hours). Quinine should never be given as an intravenous bolus and the dose must be reduced on the third day by a third or to half in patients with renal failure. The electrocardiographic QT interval must be monitored (for QT prolongation).

Table 8.30 summarises additional adjuncts to therapy for severe parasitemia with P. falciparum. The patient is monitored for the

[1] Usually three tablets, 75 mg pyrimethamine and 1500 mg sulfadoxine

[2] Usually 4 tablets of mefloquine, 1000 mg

[3] Derived from the Chinese herb *Quinghaosu*

[4] Usually 2 tablets (500 mg) every 6 hours for 3 doses

[5] An alternative regimen which requires careful monitoring but which achieves levels faster is: rapid loading dose 7 mg/kg over 30 minutes, followed by 10 mg/kg over 4 hours, and then 8 hourly maintenance doses of 10 mg/kg.

occurrence of hypoglycemia, hyponatremia, renal insufficiency and quinine toxicity. Nursing measures should be instituted for the unconscious patient; this includes nursing on the side to prevent aspiration, taping of the eyelids to prevent corneal abrasions and care of the skin. Corticosteroids are not indicated in cerebral malaria. Fits are common and some authorities recommend the prophylactic use of anticonvulsants (phenobarbitone 3.5 mg/kg i.m. single dose); convulsions should be treated with benzodiazepines or phenytoin. Exchange tranfusions have also been used with significant benefit in the treatment of cerebral malaria, although the exact indications are unclear. Severe parasitemia (>30–50% of peripheral blood) is an indication but the technique is expensive, labour-intensive and not freely available.

Prognosis Non-falciparum malaria is benign. For untreated P. falciparum infections with complications (cerebral malaria), the mortality is very high; mortality rates with treatment for cerebral malaria vary from 10–20 per cent. Neurologic recovery is usually complete. However, transient psychoses, residual coarse tremors, cerebellar signs, extrapyramidal manifestations and sixth cranial nerve palsy have all been documented after cerebral malaria. The important features which indicate an adverse prognosis in P. falciparum infections include:

1. major organ involvement (cerebral involvement, retinoscopic hemorrhages, pulmonary edema)
2. parasitemia > 20% of peripheral blood
3. laboratory abnormalities: hypoglycemia (fivefold increase in mortality), serum creatinine > 3mg/dl (doubles mortality), elevated transaminases, coagulopathy, metabolic acidosis, high CSF lactate concentrations, and
4. depth of coma.

Uncommon Sequelae of Malarial Infection

Nephrotic syndrome

P. malariae infection is causally related to a nephrotic illness. The disorder is common in Africa where children below the age of 15 years are affected, and hypertension is common. Antimalarial treatment has no effect on renal disease; combination therapy with cytotoxic drugs and corticosteriods has occasionally been effective.

Hyperreactive malarious splenomegaly (Tropical splenomegaly)

In a small minority of patients, malarial infection is associated with an aberrant immunological response; this results in hepatic sinusoidal lymphocytosis, elevated serum IgM levels and splenomegaly. This can result from infection due to any Plasmodium species and hypersplenism is common. Treatment is aimed at treating the malarial infection and is followed by lifelong chemoprophylaxis (see below).

Malaria in Pregnancy

In hyperendemic areas, malarial infection in pregnancy may be asymptomatic and associated with the significiant reduction of the birthweight of children. When maternal immunity is low, symptomatic infection ensues; this is associated with a high mortality. Hypoglycemia, pulmonary edema and fetal loss are common. Quinine treatment is generally avoided because of the propensity of the drug to cause hypoglycemia.

Malaria control[1] The National Malaria Control programme targets prompt reporting of cases, prompt diagnosis and prompt treatment of patients along with efforts to control mosquitoes and prevent breeding. These measures have been thwarted by the cost of vector control, resistance of mosquitoes to readily available insecticides such as DDT and by the emergence

[1] A malarial vaccine (using a protein SPF 66) has yielded promising results in South America but has had only limited success in Africa.

Table 8.30 Pathophysiology, complications and therapeutic approach to severe Falciparum infection

Clinical problem	*Pathophysiology*	*Treatment*
Severe parasitemia	Infection of red cells of all ages, Sequestration	Intravenous quinine, Exchange transfusion if parasitemia >50%
Hyperpyrexia	Altered temperature control, release of pyrogens	Tepid sponging, cooling blanket, fanning, monitor rectal temperature
Anemia	Erythrocyte destruction	Consider transfusion if PCV < 20%; watch out for pulmonary edema
Cerebral malaria	Sequestration	Maintain airway, prophylactic anticonvulsants, nursing care
Hypoglycemia	Not clear	50% glucose intravenous
Pulmonary edema	Sequestration with altered permeability capillaries	Diuretics with care; high inspired oxygen concentrations, PEEP
Shock (Algid malaria)	Vasodilatation, decreased effective circulatory volume	Plasma expanders, pressor agents, keep CVP 0-5 cm water
Renal failure	Sequestration, hemoglobinuria, hypotension	Consider dialysis, monitor urine output
Disseminated intravascular coagulation	Not clear	Infuse fresh whole blood, fresh frozen plasma; heparin may be dangerous

PCV = packed cell volume PEEP = positive end-expiratory pressure CVP = central venous pressure

Table 8.31 Chemoprophylaxis of malaria

Generic name	*Dose*
Chloroquine	300 mg base (usually 2 tablets) once a week, for 2 weeks before, during and for 4 weeks after exposure
Doxycycline	100 mg daily, for a few days before, during, and for 4 weeks after exposure
Mefloquine	250 mg (1 tablet) once a week, for one week before, during and for 4 weeks after exposure
Primaquine+	15 mg base once a day for 14 days; or 45 mg base once a week for 8 weeks
	Proguanil 200 mg daily (usually combined with weekly chloroquine)

+ *Gametocytocidal action* for P. falciparum malaria. To prevent potential transmission to receptive mosquitoes (can occur despite acute therapy with quinine, which does not affect gametocytes of P. falciparum) 45 mg single dose in hospital (usually on day 3).

of parasites that are resistant to cheap, safe antimalarial drugs.

Chemoprophylaxis Non-immune travellers to endemic areas may benefit from chemoprophylaxis depending on their risk of infection. The risk of infection depends on the duration of stay, the level of transmission (place and season), and the hours of potential mosquito contact. The choice of regimen depends on the prevalence of chloroquine resistance in the area and the presence of associated conditions (pregnancy, drug allergy). Table 8.31 depicts common regimens used for this purpose.

VISCERAL LEISHMANIASIS (KALA AZAR)[1]

Visceral leishmaniasis is a chronic disease caused by infection with the protozoan *Leishmania donovani* and is characterised by fever and generalised hyperplasia of the reticuloendothelial system, manifesting clinically as massive splenomegaly.

Epidemiology Visceral leishmaniasis is found widely in the eastern part of our country, especially in Bihar, Uttar Pradesh and West Bengal. It is also found in parts of Assam, Sikkim and Tamil Nadu. It is estimated that there are 1.5–2 million new cases of kala-azar globally per year. The disease is transmitted by the domestic sandfly *Phlebotomus argentipes* and the only reservoirs are humans. Epidemics of the disease are often traced to the migration of an infected individual to a new locality. In 1970 there was an epidemic in north Bihar and in the Katihar and Purnia districts of south Bihar. In the mid 1980s, there was an epidemic in the Malda and 24-Parganas districts of West Bengal. A *Mediterranean form* of the disease has been recognised; it principally affects children less than 4 years of age. It is caused by *L. infantum,* the sandfly vector is *P. perniciosus,* and dogs are the major reservoir. An *African form* of the disease is caused by the same agent but the transmitting vector is *P. martini* and rodents are important reservoirs; the clinical presence of a cutaneous lesion at the initial site of the bite (*leishmanioma*) and prominent lymphadenopathy distinguish it from the Indian form of the disease.

Pathogenesis The sandfly introduces the *promastigote* forms of the parasite into the subcutaneous tissues with its bite (which is seldom noticed). The parasites spread to the

[1] Kala azar means 'black sickness' in Hindi

regional lymph nodes and are then disseminated hematogenously within macrophages to the liver, bone marrow and spleen. The proliferation of the intracellular parasites stimulates hyperplasia of the reticuloendothelial system and provokes a granulomatous cellular immune response. This results in splenomegaly of a moderate to severe degree. Hepatomegaly is also a frequent manifestation and reflects the proliferation of amastigote-laden Kupffer cells. Lymphadenopathy is not a feature of Indian kala azar, although it is common in the African form of the disease. Involvement of the reticuloendothelial system of the gut is common; the jejunal submucosa is infiltrated with parasite-laden cells and there is associated hyperplasia of the *crypt cells* and *villous* atrophy. Bone marrow involvement is a hallmark of the disease, and parasites can be stained within the macrophages in bone marrow biopsy specimens (*LD bodies*). Bone marrow infiltration results in anemia and leukopenia. The kidneys are also involved; a subclinical immune complex mediated proliferative glomerulonephritis is not uncommon. Renal amyloidosis is a complication of longstanding disease. Involvement of the oral and nasopharyngeal mucosa (infiltration with parasitised histiocytes) is common in the Indian form of the disease.

Clinical features Kala azar has a long incubation period varying from 2–6 months (with an average of 3 months). The disease has an insidious onset, though an uncommon acute form has been described. An insidious onset of low-grade intermittent fever and symptoms related to the hepatosplenomegaly herald the onset of the disease. Fever patterns are variable: often a double quotidian pattern[1] is present. Vague abdominal discomfort, progressive abdominal distention and dull ache in the left hypochondrium are frequent complaints. Associated features include weight loss, diarrhea and a dry cough. Appetite is usually maintained early in the course of the disease. Episodes of diarrhea are common. The course is frequently punctuated by superinfection with other organisms. Bacillary dysentery may complicate it, as may pulmonary tuberculosis. Episodes of bacterial pneumonia may develop and when there is severe neutropenia, a necrotising oral anerobic infection – *cancrum oris* – may occur. Pedal edema usually reflects the hypoalbuminemia (which is part of the disease process) whereas generalised edema suggests the development of renal amyloidosis in advanced longstanding cases of the disease. Hepatic cirrhosis and portal hypertension occur in 5–10 per cent of patients.

On physical examination, the patient is weak, emaciated, with prominent trophic changes of hair (thin, dry, hypopigmented). Many patients have 'earth-grey' colour of skin (hence the name kala azar). Oral lesions appear as nodules or ulcers of the palate, gingiva or lips. Perforation of the nasal septum may result from lesions of the nasal mucosa. Hoarseness of the voice may indicate laryngeal involvement. The most impressive of the physical signs is the presence of massive splenomegaly with a moderately enlarged liver. Anemia is frequent and may explain the presence of hemic systolic murmurs.

Post-kala-azar dermal leishmaniasis

Upto 20 per cent of patients with visceral leishmaniasis develop skin lesions 2 to 10 years after successful treatment of visceral disease. These skin lesions occur predominantly on the face and to a lesser extent on the trunk and extensor surface of the arms. Initially the lesions are hypopigmented but they may enlarge to become nodular. Biopsies of skin lesions reveal a variable degree of cellular response and parasite accumulation. These subjects serve as chronic reservoirs of the disease because the lesions may last for years.

Investigations Laboratory tests reveal moderate anemia (Hb levels of 6–8 g/dl); hypersplenism, concomitant iron deficiency and

[1] Elevation of the body temperature twice daily

bone marrow depression are contributory factors. Leukopenia is characteristic, with the leucocyte count often below 3000/mm^3. There is a relative lymphocytosis and an almost complete absence of eosinophils. Hypoalbuminemia is frequent (serum albumin less than 3 g/dl) and there is an impressive polyclonal hypergammaglobulinemia (levels of 5–10 g/dl), most of which is IgG.

In the past, demonstration of the parasites in splenic aspirates was the investigation of choice. This has largely been superceded by bone marrow aspiration or liver biopsy due to the hazards associated with puncturing a large spleen. Bone marrow smears contain amastigotes (*LD bodies*) in 80–90 per cent of subjects. The parasite may be seen in the peripheral blood buffy coat smears in 90 per cent of patients if meticulously searched for. Serologic tests can help in the diagnosis of kala azar. The *formol-gel test*[1] detects high levels of IgG or IgM, lacks specificity and becomes positive only late in the disease. It may be useful as a screening test in rural centres where other tests are unavailable. The indirect fluorescent antibody test (*IFA*) and the enzyme-linked immunosorbent assay (*ELISA*) test use promasti-gotes as antigens and are positive in 95 per cent of subjects with visceral leishmaniasis.

Differential diagnosis The differential diagnosis of kala azar includes chronic malaria, typhoid fever, bacterial endocarditis, chronic myeloid leukemia, non-cirrhotic portal fibrosis and disseminated tuberculosis. Occasionally the *leishmanin test (Montenegro test)* is used to distinguish visceral leishmaniasis from some of these other diseases. The leishmanin test is a delayed hypersensitivity reaction to intradermally injected antigens prepared from cultured amastigotes. An induration of 5 mm or more, 48 hours after the injection is considered positive. The relevance of this test lies in the high negative predictive value of the positive test; a positive test rules out kala azar as the test is invariably negative in untreated visceral leishmaniasis. A negative leishmanin test does not help in the differentiation of kala azar from other diseases. The test is, however, non-standardised and is not readily available.

Treatment General measures include good oral hygiene, the provision of a nutritious diet, iron and vitamin supplementation to treat the concomitant anemia, and antibiotics to treat any intercurrent bacterial illness.

The specific chemotherapeutic regimens available are depicted in Table 8.32. Sodium stibogluconate is sometimes used for upto 40 days to reduce the relapse rates. The drug is safe and well-tolerated, though the intramuscular injections are painful. Intravenous injections should either be given slowly through a 23 gauge needle or diluted 1:10 with 5% dextrose to reduce the incidence of local thrombosis. Electrocardiographic T wave inversions are fairly common and are not an indication for cessation of therapy. However, the QT interval should be obtained twice weekly and treatment suspended if the *corrected* QT interval exceeds 0.50 seconds. Response to the treatment is monitored by assessment of fever, weekly monitoring of hemoglobin levels and splenic size, and by bone marrow aspirate smears and cultures at the end of the treatment period. Usually fever disappears first (7–10 days), followed by a rise in hemoglobin and a decrease in splenic size (2 weeks). If fever persists, concomitant tuberculosis should be suspected. The spleen regresses slowly and becomes non-palpable within 6–12 months. Relapses occur in about 1–13 per cent of cases. An increase in splenic size, a fall in eosinophil count to less than 50/mm^3 and a fall in hemoglobin levels suggest a relapse and this should be confirmed with examination of bone marrow aspirates.

Treatment of post-kala azar dermal leishmaniasis with pentavalent antimonials

[1] Chopra's aldehyde test is based on the same principle of detecting hyperglobulinemia.

results in improvement of skin lesions, though the pigmentation may persist indefinitely. In the African form of the disease this condition resolves spontaneously.

Prevention and control In India the incidence of kala azar diminished dramatically during the malaria eradication programme but has risen again with the cessation of spraying of DDT. This suggests that control of the sandfly vector can reduce disease rates. Since humans are the only reservoirs in our country, proper treatment of all diseased individuals is necessary to decrease the community load of the parasites.

AMEBIASIS

Amebiasis refers to an invasive disease of the intestines or extraintestinal tissues, due to the protozoan *Entamoeba histolytica.*

Epidemiology It has been estimated that upto 10 per cent of the world population is infected with *E. histolytica.* However, only 10 per cent of infected individuals develop clinical invasive disease. The majority of infections are found in developing countries where the disease is predominantly spread by *indirect* methods due to poor sanitary

Table 8.32 Treatment of kala azar

Category	*Drug*	*Dose*	*Comments*
Drug of choice	a. Sodium stibogluconate (Pentostam, 100 mg antimony/ml)	20 mg Sb/kg/day iv or im x 20–28 days (preferably divided into 2 daily doses)	• side effects include arthralgia, bradycardia, diarrhea, rash, elevated amylase levels
	or		• 40 day courses have been recommended as Sb resistance occurs in 10%
	b. Meglumine antimonate (85 mg antimony/ml)	20 mg Sb/kg/day iv or im x 20–28 days	
Alternative for relapses/ treatment failure	c. Pentamidine isethionate	2–4 mg/kg daily or every other day im for 15 doses.	• >90% cure • hypoglycemia in 10% • permanent DM 4%
Newer drugs (experimental at present.	d. Gamma interferon plus a) or b)	100 mg/day for 10–20 days	prohibitively expensive
	e. Amphotericin B	0.5 mg/kg/day for 14 days; iv slow infusion	• low dose used, decreases side effects, >90% cure • liposomal complexes less toxic
	f. Ketoconazole	600 mg/day p.o x 28 days	• 80% cure reported
	g. Aminosidine (paromomycin) plus a) or b)	15 mg/kg/day for 20 days	• >80% cure rate

Sb = antimony DM = diabetes mellitus

conditions. Amebiasis is transmitted by eating contaminated vegetables grown in soil fertilised by human excreta and is common in areas where household pests (such as fleas and cockroaches) have access to human feces and food. Water-borne epidemics have been attributed to fecal contamination or faulty plumbing. In developed countries the parasite may be spread by the sexual mode in homosexual individuals. The source of the organisms is usually the large number of individuals who carry cysts of *E. histolytica* but have no disease– the *asymptomatic cyst passers.* Children, pregnant women and individuals receiving steroids are especially susceptible to invasive amebiasis. Pathogenic and non-pathogenic strains of *E. histolytica* have been described based on the patterns of isoenzymes[1] produced, but such analysis is primarily a research tool.

Pathogenesis Two forms of *E. histolytica* are described. The cyst is the infective form of the organism that resists environmental conditions. Once ingested, the organism excysts in the lumen of the lower small intestine and the other form, the trophozoite, is liberated. The trophozoites penetrate the mucous membranes in regions of maximal fecal stasis: the cecum, ascending colon and the rectosigmoid colon. The organisms form small submucosal abscesses that soon lead to mucosal sloughing with the formation of the classical *undermined flask-shaped ulcers* without ragged edges. The trophozoites also enter the portal venous radicles and reach the liver where they can cause abscess formation. The selective streaming of blood in the portal circulation explains the greater frequency of involvement of the right lobe of the liver. Further spread occurs by contiguous spread from the liver or by the hematogenous route.

[1] Also called *zymodemes*

Intestinal Disease

Clinical features Four major intestinal syndromes related to amebiasis are described. The most common form of the disease is *asymptomatic cyst passage.* Most asymptomatic cyst passers do not develop disease and spontaneously stop shedding cysts without any drug treatment. They are the most important sources of infection. *Acute amebic colitis* is the second commonest presentation and can present as a spectrum of disease that ranges from a mild painful diarrhea to a frank *dysenteric* illness. Classically, the patient complains of cramping lower abdominal pain along with the passage of fluid or semi-fluid stools (about 7–10 in number per day) with blood and mucous. The presence of tenesmus usually suggests rectal involvement. The important signs are fever (33%) and abdominal tenderness (80%). Inflammation of the appendix and cecum may mimic appendicitis (*amebic typhlitis*). *Fulminant colitis* is an uncommon presentation seen usually in children. It presents with profuse bloody diarrhea, fever and diffuse abdominal pain. Concurrent liver abscesses are common as are multiple colonic perforations (75%). Toxic megacolon[2] is a rare complication. A rare manifestation of intestinal amebiasis is the development of an inflammatory bowel mass usually in the right iliac fossa—an ameboma. An ameboma may present as an asymptomatic lump mimicking a colonic neoplasm or it may be tender and associated with symptomatic dysentery. A fifth bowel manifestation of amebiasis is postdysenteric colitis—persistent diarrhea lasting several months after an episode of amebic dysentery. However, this entity is controversial and its existence has been debated.

Laboratory diagnosis The diagnosis of amebic colitis is established by examination of wet mounts of the stool specimens. Diagnosis is made with the identification of hematophagous[3]

[2] Condition characterised by colonic distension with intramural gas

[3] With intracellular red cells; also called erythrophagocytic

trophozoites in the absence of fecal leucocytes. Three to six stool specimens may have to be examined for a diagnosis to be made. The yield is higher if sigmoidoscopy is performed and the edges of the colonic ulcers are scraped and examined for the presence of trophozoites. Serologic tests may also be helpful if the stool examinations are inconclusive. The four tests available are: indirect hemagglutination assays (IHA), agar gel diffusion (AGD), ELISA and counterimmunoelectrophoresis (CIEP). Whereas IHA tests are persistently-positive for upto 10 years after an attack of amebic colitis, the other tests typically become negative within 6–12 months of an episode of colitis. Radiologic tests play no role in the diagnosis of amebic colitis.

Differential diagnosis Amebic colitis must be distinguished from bacterial colitis (due to *Shigella, Salmonella, E. coli, Yersinia, and Campylobacter* species) and from inflammatory bowel disease. The stools in amebic colitis are more fecal, less watery, contain tenacious mucous and fresh and altered blood, and do not contain a large number of leucocytes as compared to bacterial colitis. Since considerable similarity exists in the clinical presentations, stool examination (for amebae, bacteria), stool cultures (for bacteria) and amebic serology are the only reliable means to differentiate between these entities.

Treatment The treatment regimens for intestinal amebiasis are shown in Table 8.33. The importance of using luminal amebicides after an attack of dysentery must be emphasised because metronidazole has limited activity against cysts.

Extraintestinal Disease

Amebic liver abscess

Clinical features Amebic liver abscess is the most common extraintestinal manifestation of amebiasis. Men are affected more often than women and the peak incidence is in the third to fifth decades. The right lobe of the liver is involved five times more often than the left lobe. The consumption of alcohol brewed illegally under unhygienic conditions is a predisposing factor.

The presentation of amebic liver abscess may be acute (clinical history <10 days) or more commonly, subacute (symptoms lasting from 2–6 months). The most common presenting complaint is pain in the right hypochondrium. The pain is often dull but may be pleuritic and may be referred to the right shoulder. A dry cough is a common complaint and signifies pleuropulmonary irritation due to the subdiaphragmatic pathology. Fever is almost universal in the acute presentation but is present only in a third of patients with a subacute presentation. A concomitant diarrheal illness may be present in 20–30% of patients. The important physical signs include a *tender hepatomegaly* (30–60%, being more common in subacute disease), a *diminished excursion of the right hemidiaphragm*[1] and intercostal tenderness (elicited by gently palpating the intercostal space). A pleural friction rub may be heard and may either denote a sympathetic serous pleural effusion (more common) or indicate trans-diaphragmatic rupture of the abscess into the right pleural space. A bulge on the right chest wall is an uncommon sign and may indicate *pointing* of the abscess into the subcutaneous tissues. Clinical jaundice is uncommon and is a poor prognostic sign.

The clinical presentation of left lobe abscesses is often different from that of right lobe infections. Epigastric pain and a palpable epigastric mass are more common and these abscesses are more dangerous due to their potential for rupture into the pericardial space.

[1] This combination of findings is called *right base pathology* and the differential diagnosis includes subdiaphragmatic disease or inflammation of the right lower lobe (consolidation, tuberculosis, hydatid disease etc.).

Diagnostic procedures Polymorphonuclear leucocytosis (10,000–20,000/mm^3) is common (60%). Levels of transaminases are normal in 50 per cent of those with acute disease and in 75 per cent of those with subacute disease. The levels are usually less than 100 IU even when they are elevated. Alkaline phosphatase levels are elevated in 75 per cent of patients. Serologic evidence of amebiasis is seen in the majority of patients. The chest X-ray demonstrates a right pleural effusion and an elevated right hemidiaphragm.

The investigation of choice is an ultrasound scan of the liver. The abscess appears as a round hypoechoic or anechoic area without significant wall echoes and is contiguous with the liver capsule. The abscess is solitary in about 70–80 per cent of patients. CT scans are also sensitive for demonstrating the abscess but are expensive. Sonography has the advantage of being inexpensive, and of easy repeatability to assess disease progress or resolution. In two-thirds of patients the hepatic sonogram normalises in appearance in 6 months.

Differential diagnosis Pyogenic liver abscess, a necrotic tumour and hydatid cysts are the other diagnostic possibilities; the clinical presentation of the latter two diseases is different and they enter into the differential diagnosis based on the sonographic appearance. A multiplicity of abscesses, occurrence in an elderly subject, the presence of a condition predisposing to bacteremia (such as recent abdominal surgery) may raise the suspicion of a pyogenic abscess. When the possibility of a pyogenic abscess is high, a diagnostic aspiration of the abscess must be considered. The aspirated pus seldom, if ever, demonstrates trophozoites (in amebic abscess) but bacteria may be readily identified (in pyogenic abscesses).

Treatment The treatment regimens that may be used for treating an amebic liver abscess are listed in Table 8.33. Defervescence occurs in 3–5 days. Some authorities combine these regimens with an antibiotic to combat any secondary pyogenic infection. Secondary infection of an amebic liver abscess is rare in the absence of attempted aspiration (when it may be 0–15%). Randomised clinical trials have failed to reveal any advantage of aspirating an amebic liver abscess, over simple medical treatment. Indications for aspiration are: 1) for diagnostic purposes if a pyogenic abscess is likely; 2) failure to respond to medical therapy in 5–6 days; and 3) when rupture is imminent, especially for a left lobe abscess. Surgical drainage has not been shown to have any benefits over medical treatment and carries the risk of secondary infection and prolonged drainage from the incision site.

Complications 1. Pleuropulmonary involvement is the commonest complication of an amebic liver abscess, and is encountered in 20–30 per cent of patients. The involvement is in the form of a spectrum of manifestations ranging from a serous sympathetic effusion, a consolidation, lung abscess, amebic empyema to the formation of a hepatobronchial fistula. Thoracentesis is essential to establish the type of pleural pathology. Serous effusions resolve spontaneously. Contiguous transdiaphragmatic spread with the formation of a pulmonary abscess or a consolidation usually responds adequately to medical therapy aimed at the liver abscess. Rupture into the pleural cavity tends to present more dramatically with sudden onset of pleuritic pain and dyspnea and may require drainage. The formation of a hepatobronchial fistula begins as a cough with expectoration of reddish-brown sputum[1] which may contain amebae.

2. Peritoneal rupture is the second commonest complication of an amebic liver abscess, occuring in 2–5 per cent of patients. Slow indolent leaks are more common than sudden ruptures. The condition is amenable to medical therapy with percutaneous catheter drainage.

3. Intrapericardial rupture is uncommon but is one of the most serious complications

[1] Called anchovy sauce material

Table 8.33: Drug treatment of amebiasis

Infection category	*Drug*	*Dosage*	*Comments/Side effects*
I Asymptomatic cyst passer	iodoquinol (previously Diodohydroxyquin)	650 mg p.o tid x 20 days	side effects of iodoquinol: • nausea, abdominal cramps, maximum dose 2 g/day. • optic atrophy with prolonged use, ECG change
	or		
	Paromomycin	500 mg p.o tid x 7 days	• This is an aminoglycoside; can cause vertigo
	or		
	Diloxanide furoate	500mg p.o tid x 10 days	
II Mild to moderate diarrheal disease	metronidazole or tinidazole	750 mg p.o tid x 10 days	side effects of metronidazole metallic taste common • very dark urine • avoid alcohol • avoid in 1st trimester of pregnancy • headache
		1 g p.o bd x 3 days	
	followed by		
	iodoquinol or paromomycin	650 mg p.o tid x 20 days 500 mg p.o tid x 7 days	
III Dysenteric disease	metronidazole or tinidazole or dehydroemetine	750 mg p.o x 10 days 600 mg p.o bd x 5 days 1–1.5 mg/kg/d im x 5 days	
	followed by		
	iodoquinol or paromomycin	650 mg p.o tid x 20 days 500 mg p.o tid x 7 days	
IV Extraintestinal (hepatic abscess)	metronidazole or tinidazole	750 mg iv or oral tid x 10 days 800 mg tid x 5 days	
	followed by iodoquinol	650 mg p.o tid x 20 days	
or	dehydroemetine (DHE)	1.5 mg/kg/day im x 10 days	Side effects of DHE • max of 90 mg/day • ECG changes monitored • peripheral neuropathy
	followed by		
	chloroquine phosphate + iodoquinol	600 mg base (1 gram)/day x 2 days followed by 300 mg base (500 mg)/d x 20 days 650 mg p.o tid x 20 days	• avoid strenuous exercise for 4 weeks after treatment

Tinidazole is a nitroimidazole compound similar to metronidazole that is at least as effective as the latter drug and is better tolerated.

of an amebic liver abscess. The presentation is often dramatic with the onset of cardiac tamponade and shock. Clinical suspicion must be high in any patient with an abscess of the left lobe of liver who develops hypotension. Echocardiography is diagnostic and open drainage is the treatment of choice because of the development of loculations. The condition is associated with a high mortality (40%).

Other extraintestinal sites of disease

Cerebral amebiasis (< 1% in autopsy series) and renal amebiasis are rare extraintestinal sites of amebiasis.

Prevention of Amebiasis

Eradication of vectors such as houseflies, hygienic practices such as keeping food covered, boiling the water used for cooking and avoiding consumption of raw vegetables can reduce the incidence of amebiasis. Those cooking meals for a large number of people must periodically undergo stool examinations for detecting asyptomatic cyst passers who are the reservoirs of infection. Avoiding drinking illegally brewed alcohol and restricting the use of night soil as fertiliser are other important measures.

GIARDIASIS

Giardiasis is an infection of the small intestine by the pear-shaped flagellated protozoan *Giardia lamblia.* The organism is associated with a wide range of clinical manifestations ranging from asymptomatic infection to severe diarrhea.

Epidemiology Giardiasis is widely prevalent in developing countries; estimates vary from 10–20 per cent of the population in these countries. The disorders is three times more common in children as compared to adults. Transmission is by the feco-oral route; food and water are common media for transmission of the organism. The organism can also spread directly by intimate contact in children and by a sexual mode in homosexuals.

Pathogenesis Cysts of giardia are resistant to adverse environmental conditions and are the infective forms. After ingestion, the organism excysts in the duodenum and jejunum and the trophozoite forms multiply by binary fission. The trophozoites can cause mechanical damage to the mucosa, can alter intestinal motility, encourage bacterial overgrowth directly, deconjugate intestinal bile salts and can provoke a T cell mediated immunological damage to the mucosal brush border. The end result is a malabsorption syndrome with a diminution in the mucosal villus/crypt ratio.

Disorders with immunodeficiency are frequently associated with giardia infection. Travellers and patients who have undergone gastrectomies are other groups with an increased frequency of giardia infection.

Clinical features Giardiasis is most often asymptomatic. About a third of infections are symptomatic. The initial symptom may be an episode of acute profuse watery diarrhea with abdominal cramps. The stools are foul-smelling and greasy; mucous and blood are absent. This episode is usually self-limiting and lasts for 5–10 days. Chronic giardiasis presents as flatulence, bulky malodorous stools and epigastric pain. Young children may suffer significant growth retardation.

Diagnosis No clinical feature is diagnostic of giardiasis; the diagnosis is based on identification of the organism in the stools. In chronic giardiasis, repeated stool examinations may have to be performed as there may be very few organisms in the stool specimens. Duodenal contents may be examined for the parasite if the diagnostic suspicion is high and if repeated stool examinations are negative. A nylon string can be passed into the duodenum from the mouth. The organism may attach itself to the string, which should be examined for trophozoites. Alternatively, endoscopic aspirates of duodenal contents can be examined for trophozoites.

Treatment Metronidazole (250 mg tid oral for 5 days), tinidazole (single oral dose of 2 grams) and quinacrine (100 mg orally tid after meals for 5 days) are all very effective for treating giardiasis. Furazolidone (8 mg/kg/day in four divided doses) is an alternative in young children. Besides symptomatic individuals, asymptomatic cyst passers should also be treated.

Other protozoal infections are summarised in Table 8.34.

Table 3.34 Less Common protozoal infections

Disease	*Etiology*	*Epidemiology*	*Symptoms*	*Diagnostic tests*	*Treatment*
Toxoplasmosis	Toxoplasma gondii: a sporozoan	ingestion of raw undercooked meat containing cysts, exposure to soil contaminated with cat feces; transplacental transmission	• **congenital:** neonatal jaundice, hepatosplenomegaly, chorioretinitis, blindness, mental retardation, thrombocytopenic purpura, intracerebral calcification. • **adult:** fever, cervical lymphadenopathy, chronic chorioretinitis, encephalitis (especially in HIV+)	serology with detection of IgM antibodies by the indirect fluorescent antibody test	Sulphadiazine 5–6 g po/day x 4–5 weeks + Pyrimethamine 100 mg po followed by 25 mg po/day x 4–5 weeks. Double dose and add folinic acid 10 mg qd in HIV+ patient
Babesiosis	Babesia microti: a sporozoan	common in domestic animals; humans are accidental hosts; hard ticks (Ixodes sp.) transmit the illness.	fever, anemia, jaundice, hemoglobinuria, renal failure.	intraerythrocytic parasites with tetrads and basket forms	Quinine 650 mg p.o. tid x 7 days + Clindamycin 1.2 g i.v. bd x 7days
Coccidiosis	Isospora belli and Sacrocystis hominis	Feco-oral route; humans are accidental hosts; especially. Common in HIV+	mild diarrhea, abdominal pain	parasite in stool	Trimethoprim (160 mg) and Sulfamethoxazole (800 mg) qid x 10 days, then tid x 3 weeks

Table 8.34 Less common protozoal infections (contd.

Disease	*Etiology*	*Epidemiology*	*Symptoms*	*Diagnostic tests*	*Treatment*
Cryptosporidiosis	Cryptosporidium parvum: a sporozoan	children in day-care centres, HIV+ individuals	• **immunocompetent** host: profuse watery diarrhea (acute). • **immunocompromised** host: chronic diarrhea, pneumonia	acid-fast parasites in stools; serology	None effective
Balantidiasis	Balantidium coli: a ciliate	acquired by drinking fecally contaminated water	asymptomatic to diarrhea or dysentery	Trophozoite or cyst in fresh stool specimen	Tetracycline 500 mg qid p.o. x 10 days
Trypanosomiasis (sleeping sickness)	Trypanosoma gambiense and T.rhodesiense (African form) T. Cruzi (South American form): Both are hemoflagellates	**African form:** transmitted by tsetse fly (*Glossina*) **S. American:** Reduvid bug	**African form:** fever, headache, lymphadenopathy, cutaneous eruptions, localised edema, coma **S. American form** (Chagas disease): fever, lymphadenopathy, hepatosplenomegaly, facial edema. **Complications:** cardio-myopathy, megaesophagus, megacolon	**African form:** found in blood smears and CSF stained with Giemsa **S. American form:** not found in blood	T. Brucei: 1) Early infection (normal CSF): Suramin 20 mg/kg on days 1,3,7,14,21 (after test dose of 0.2 g iv) 2) Late (CSF abnormal) Suramin 0.2 g/day x 2 doses followed by Melarsoprol (trivalent arsenical) 0.4 mg/kg iv/day increased to 3.5 mg/kg/day over 4 weeks T. Cruzi: Nifurtimox: 8–10 mg/kg/day/oral x 4 months or Benznidazole 2.5 mg/kg bid oral x 2 months

KEY CONCEPTS

Malaria

- This disease is endemic in the tropics. It is caused by one of four *Plasmodium* species which are transmitted by the female *Anopheles* mosquito. Sporozoites injected into the bloodstream mature in hepatocytes and then infect and destroy red blood cells.
- The clinical hallmark is *paroxysms of fever with chills* (periodicity varying with species and disease duration). Associated symptoms such as malaise, headache and myalgia are common. Splenomegaly is the most important clinical sign.
- P. falciparum infection often runs a malignant course with complications: *cerebral* malaria (due to intracerebral sludging of sticky parasitised RBCs), renal failure (*black water fever*) and shock (*algid* malaria).
- Giemsa-stained thick smears help identify the presence of the malarial parasite in blood; thin smears are required for identification of the species.
- *Treatment* is with oral chloroquine in uncomplicated illness due to non-falciparum infection; alternative options in areas with *chloroquine resistance* include pyrimethamine-sulfadoxine/mefloquine. For treatment of P. falciparum infections in areas with high prevalence of chloroquine resistance, parenteral quinine is preferable. Steroids are contraindicated in cerebral malaria. For P. vivax and P. ovale infections, primaquine is additionally recommended (in non-pregnant patients) for eradication of exoerythrocytic parasites; testing for G-6 PD is recommended prior to the use of primaquine.
- *Prophylaxis* for a non-immune traveller to an endemic area is with weekly chloroquine (started 2 weeks prior to the visit); mefloquine or doxycycline can be used for malaria prophylaxis in areas with chloroquine resistance.

Kala azar

- Visceral leishmaniasis is due to the protozoan *Leishmania donovani*. The illness is endemic in parts of India and is transmitted by the sandfly *Phlebotomus argentipes/sergenti*. Children and young adults are most often affected.
- The organism after infection localises in the reticuloendothelial system where it causes hyperplasia of splenic/tissue macrophages, hepatic Kupffer cells and monocytes.
- The disease manifests clinically with fever, moderate splenomegaly with hepatomegaly, weight loss, abdominal distension, emaciation, and a darkening of the complexion. Bacterial superinfection is common (tuberculosis, shigellosis, cancrum oris).
- Laboratory investigations reveal anemia with pancytopenia and hyperglobulinemia. A definitive diagnosis requires demostration of *LD bodies* in a buffy coat smear, bone marrow biopsy or a liver biopsy.
- The treatment consists of a course of pentavalent antimonials or pentamidine.

Amebiasis

- This is an infection due to *Entamoeba histolytica;* its spread is by the feco-oral method in areas with poor sanitation
- The disease may be *asymptomatic* (cyst passers), *intestinal* or *extraintestinal.* Intestinal disease varies in severity from a mild diarrheal illness to severe dysentery. Crampy abdominal pain is a frequent accompaniment. Complications include perforation and formation of an ameboma (RLQ mass).
- The extraintestinal disease is often an *amebic liver abscess.* Such abscesses are usually single and are more common in the right hepatic lobe. Associated clinical features include fever, tender hepatomegaly, *intercostal tenderness,* a variable degree of icterus and a right-sided pleural effusion. Complications of a liver abscess include rupture into the pleura/pericardium or peritoneum.
- The diagnosis of intestinal disease is by stool examination. A liver abscess can be demonstrated with US; positive serology (80%) corroborates the diagnosis. LFTs may be deranged with increases in bilirubin, alkaline phosphatase and transaminase levels.
- Treatment of *intestinal disease:* for asymptomatic cyst passers diloxanide furoate is used; for symptomatic disease, metronidazole is combined with a luminal amebicide (iodoquinol). The treatment of extra-intestinal disease is with the above regimen, or with choloroquine + emetine + iodoquinol.

Giardiasis

- The etiologic agent is the protozoan *Giardia lamblia* which is endemic in the tropics. Infection is acquired via the feco-oral route by ingestion of food contaminated with cysts.
- The symptoms vary: asymptomatic carriage, diarrhea, malabsorption syndrome.
- The diagnosis is by demonstration of the organism in stools or duodenal contents (*string test*).
- The treatment is with metronidazole/quinacrine/furazolidine.

8.10 Helminthic diseases

General considerations Helminthic parasites belong to two phyla: Nemathelminthes, which includes nematodes (roundworms), and Platyhelminthes, which includes cestodes (tapeworms) and trematodes (flukes). Helminthic parasites differ from protozoan parasites in being multicellular worms, having a free-living stage outside the host, and by their tendency to excite an eosinophilic response within the hosts.

INTESTINAL NEMATODES

Hookworm

Epidemiology Infection with hookworm, either Ancylostoma duodenale or Necator americanus, is widely endemic in tropical and subtropical countries where sanitary disposal of human feces may not be practised (thus permitting human fecal contamination of the soil), where the soil is damp enough for larval survival, and where human contact with contaminated soil is likely. Individuals at risk include children and farmers who walk barefoot over night soil. Ancylostoma duodenale infection is more common in north India and Necator americanus is frequent in south India.

Pathogenesis Hookworm eggs excreted in feces hatch in the soil in 7–10 days, releasing rhabditiform larvae which develop into infective filariform larvae. Percutaneous larval penetration is the principal mode of human infection, but infections with A. duodenale may also be acquired by oral ingestion. Larval penetration of the skin often produces a pruritic, maculopapular eruption at each site of entry (ground itch). From the skin, hookworm larvae travel through the bloodstream to the lungs. Hookworm larvae enter the alveoli, ascend the tracheobronchial tree up to the pharynx, are swallowed and then reach the small intestine, where they attach themselves to the gut wall. The larvae mature in the intestine into adult worms which produce eggs in about 6 weeks.

Clinical features The major health impact of hookworm infection is iron loss, resulting from the 0.1 (Necator) to 0.4 ml (Ancylostoma) of blood ingested daily by each adult worm. In malnourished hosts, such blood loss can lead to severe iron deficiency anemia. Larvae and young adult worms in the intestinal tract may cause gastrointestinal symptoms, including nausea, vomiting, abdominal pain and increased flatulence. Transpulmonary larval passage may elicit a transient eosinophilic pneumonitis.

Investigations Intestinal infection with hookworm is usually easily diagnosed by identifying hookworm eggs in stool examinations.

Treatment Mebendazole (100 mg twice daily for 3 days), albendazole (400 mg single dose) or pyrantel pamoate (11 mg/kg/day for 3 days) are effective against hookworms. Bephenium hydroxynapthoate (5 g orally followed 2 hours

later by a saline purge) and tetrachlorethylene (3 ml) are effective alternative drugs. Anemia caused by hookworm responds to iron. Follow-up stool examinations are indicated after 2 weeks and therapy may be repeated if a heavy worm burden persists.

Ascaris

The roundworm, Ascaris lumbricoides, is the most prevalent intestinal helminthic parasite worldwide.

Epidemiology Roundworm infection can occur at any age but infection is highest in children between ages 3–8 years. Most transmission occurs by the ingestion of infective eggs on dirty hands in fecally-contaminated agricultural produce or through geophagia.[1] Infection is more common in areas with poor sanitation, where children fecally pollute the soil.

Pathophysiology The swallowed eggs hatch in the intestine and molt into larvae, which penetrate the gut wall and reach the lungs hematogenously. Larvae from the capillary bed penetrate the alveoli, develop further and then ascend the tracheobronchial tree. They are swallowed, and return to the small intestine. There the larvae mature into adult male and female worms. The fertilised adult female produces up to 2,00,000 eggs a day, which are passed in the feces. These eggs are quite resistant to the environment and can remain viable for up to five years. Under warm and humid conditions, the fertilised eggs become embryonated and infective.

Clinical features The clinical manifestations of ascariasis may occur during the early phase of transpulmonary migration of the larvae or with established intestinal infections. During the initial migratory phase, wheezing, coughing, and fever may occur, along with peripheral blood eosinophilia and transitory pulmonary infiltrates. The large adult worms in the intestine usually cause no symptoms, although heavy parasite burden may aggravate nutritional deficiency. Live worms may be passed in the stools and may be the first recognised sign of infection. Infrequently, adult Ascaris worms may cause serious complications. In heavy infections, especially in children, the adult worms may cause partial or complete intestinal obstruction. Sometimes adult worms may migrate from their normal location within the intestinal lumen into the biliary tract or appendix; obstruction of these organs can manifest as acalculous cholecystitis, cholangitis, pancreatitis or appendicitis.

Diagnosis Intestinal infections with roundworm can be diagnosed by identifying the eggs in stool examinations.

Treatment Mebendazole (100 mg bid for 3 days), albendazole (400 mg single oral dose), pyrantel pamoate (11 mg/kg single dose) are all effective agents. Mebendazole and albendazole should be avoided during pregnancy or if heavy Ascaris infection is suspected (these drugs may cause migration of adult worms). Piperazine citrate (75 mg/kg, maximum of 3.5 g, for 2 days), which paralyses the worms, is the anthelminthic drug of choice in this situation. Recent studies suggest that in endemic areas mass treatment may be preferable to selective treatment. Levamisole (120 mg or 2.5 mg/kg, single dose) is the preferred agent for such mass treatment.

Pinworm Infection

Pinworm infection is due to the intestinal nematode *Enterobius vermicularis.*

Epidemiology Pinworm infection is acquired by ingestion of infectious eggs by direct transfer from the anus to the mouth of the same person, or indirectly through contaminated clothing, food or household articles. Prevalence is highest

[1] In regions with large concentrations of Ascaris eggs in the soil, eggs may be disseminated in the dust and may be inhaled.

in children of school-going age. Infection of several members within the same family is common.

Pathogenesis Larvae from ingested eggs are found in the small intestine; young worms mature in the cecum and upper colon. Gravid female worms migrate into the rectum and discharge eggs in the perianal skin.

Clinical features Pinworm infection may be asymptomatic. When symptoms do occur, the cardinal symptom is perianal itching, which is often worse at night when the worms migrate. Disturbed sleep, and secondary infection of scratched skin are other complaints. Infrequently, the migration of adult worms into or through the female genital tract results in vulvo-vaginitis, salpingitis or peritoneal inflammation associated with granuloma formation.

Diagnosis Since pinworm eggs are deposited on the perianal skin, stool examinations are usually negative. Pinworm infections are diagnosed by applying cellulose acetate tape to the perianal skin in the morning (preferably before defecation or bathing) and examining the tape microscopically for eggs; the tape is placed on a slide with a drop of toluene between the tape and the slide (this dissolves mucilage and dispels air bubbles, thereby improving visualisation of ova).

Treatment Mebendazole (100 mg single oral dose), albendazole (400 mg single oral dose), pyrantel pamoate (11 mg/kg single oral dose) are all effective against pinworm infection. Treatment should be repeated after two weeks because reinfection is common. Personal hygienic measures such as washing hands before eating or preparing meals, frequent baths, frequent change of underclothing and the clipping of fingernails should also be instituted to reduce the opportunities for reinfection.

Filariasis

Filariasis is an infective disease caused by one of two filarial nematodes (*Wucheraria bancrofti* or *Brugia malayi*). It manifests as acute lymphangitis which is followed by chronic inflammation and obstruction of lymphatics.

Pathogenesis Our knowledge of the pathogenesis of filarial disease has been further refined recently. After filarial infection, newly exposed people (for example, visitors to an endemic area) often develop acute lymphatic inflammation, followed by chronic sequelae. However, people with chronic exposure to the organism may not always develop acute manifestations of disease. The filarial parasite induces what is termed a '*parasite-specific immunosuppression*'; some people will develop only asymptomatic microfilaremia and serve as vectors of the parasite but never develop clinical disease. Others develop a largely subclinical lymphatic dysfunction characterised by lymphatic dilatation but little if any inflammation. Some others (those with intact antifilarial immune response) may manifest acute and chronic inflammation of the lymphatics.

Epidemiology Lymphatic filariasis is a disease of developing countries. The tropical regions of the world are especially affected, with the majority of cases being reported from southeast Asia, the Pacific and eastern Africa. It is estimated that in India there are 374 million people living in endemic areas and, of these, 45 million people are infected. Bancroftian filariasis is more common (85–90%) and endemic through most of southern, central and eastern parts of the country. Brugian filariasis (15%) is mostly found in Kerala, but scattered foci have been reported in Orissa, Assam, Madhya Pradesh, Andhra Pradesh and Tamil Nadu. A focus of subperiodic Bancroftian filariasis has been described in the Nicobar islands. The mosquito vectors for filariasis include Culex, Anopheles, and Aedes species.

The Mansonia species can additionally serve as a vector for Brugia malayi.

Clinical features The clinical features of the early stages of filariasis can be divided into those which are inflammatory and those which are obstructive (Fig 8.16). Considerable overlap may occur between these stages. The earliest phase of inflammation consists of local reactions—lymphangitis, lymphadenitis and abscess formation. If a lymphatic vessel is affected in a limb, the attack begins with local pain, swelling or redness of an arm or a leg. The inflammation may be unilateral or bilateral. In the legs the femoral and malleolar vessels are most frequently affected. A 'focal spot' of pain and tenderness in the region of the malleoli is followed by an ascending, retrograde lymphangitis. In other instances, the lymphangitis starts near the femoral lymph glands and spreads centrifugally (downwards in the leg). The affected vessels are acutely tender, easily palpable and visible as bright red streaks due to the overlying skin becoming inflamed and erythematous. Stiffness of an involved extremity is common. Local lymphadenitis, with enlargement of the epitrochlear, the axillary, the femoral or the inguinal nodes (depending upon the site of infection) frequently accompanies these early symptoms. Systemic manifestations are few and include mild fever. Typically, the acute local manifestations subside over the course of a few days, with the enlargement of regional lymph nodes persisting. Thereafter, attacks are recurrent over periods of a few weeks to several years. Involvement of the visceral lymphatics of the pelvis, abdominal or retroperitoneal areas manifests predominantly as fever along with constitutional symptoms. Such febrile attacks are characterised by high grade temperature of the order of 40°C or more and are referred to as 'filarial fever' or 'elephantoid fever'. Occasionally, small abscesses may form in the affected vessels or glands and discharge on the surface, forming sinuses. The site of an abscess is indicated by extreme tenderness over the area, the abscess itself being deep seated in intermuscular fascial planes. Orchitis (inflammation of the testes), funiculitis (lymphangitis of the spermatic cord) and epididymitis are common complications of Bancroftian filariasis. Orchitis begins with sudden severe disabling testicular pain, with the testicle enlarging rapidly and becoming extremely tender. It is often unilateral and is sometimes associated with an acute hydrocele. Funiculitis and orchitis tend to recur and subside spontaneously. The thickening of the spermatic cord is one of the earliest signs of filariasis and must be carefully sought. The obstructive phase of filariasis is characterised by interference with the lymphatic circulation, development of edema and the accumulation of serous fluid in the infected tissues. The affected lymph nodes may become soft and lobulated and the lymphatic vessels involved become tense and distended with fluid— lymph 'varices'. The varicose vessels become mingled with the local enlarged lymph nodes, forming an irregular mass of tissue—'varicose glands'. The lymph nodes are usually discrete but necrosis following secondary infection can lead to a matted appearance. The lymph drainage of the scrotal area is frequently obstructed and consequently the scrotal skin and subcutaneous tissues become edematous. The skin over the scrotum appears erythematous and is covered with small vesicles containing clear or milky fluid (commonly containing microfilariae). The vesicles continually rupture and reform so that the scrotal surface is constantly wet; this state is termed a 'lymph scrotum'. The thickened scrotal skin gradually becomes greatly coarsened, eventually passing on to 'elephantiasis'. The gradual accumulation of fluid in the cavity of the tunica vaginalis leads to the formation of a hydrocele. The fluid may be clear or milky but usually contains microfilariae. Obstructed varicose lymph vessels in the retroperitoneum may rupture into the urinary tracts with

their contents leaking into the renal pelvis, the ureters or the urinary bladder. The resulting clinical picture – chyluria – is frequently dramatic. There is often a history of preceding loin pain or of pain in the back followed by the passage of a milky urine. Milky urine is passed for 2 or 3 days at a time before it subsides, only to recur after an interval of weeks or years. Occasionally, the lymphatics which rupture into the urinary tract contain lymph (and not chyle), leading to the passage of blood-stained urine containing lymph; this state is termed *lymphuria*. Rarely, the lymph or chyle may rupture into the peritoneal cavity giving rise to 'lymphatic' or 'chylous' ascites. In the extremities, lymphatic obstruction results in a soft pitting edema (Grade 1 lymphedema) which resolves between attacks. With the progression of disease, a chronic persistent non-pitting lymphedema (Grade 2 lymphedema) results that eventually gets transformed into the woody induration characteristic of elephantiasis. Elephantiasis may on occasion involve the mammae or the vulva. The skin epithelium hypertrophies and wart-like thickenings appear (Grade 3 lymphedema). The subcutaneous tissue is replaced by myxomatous fibrous tissue and the patient finds it difficult to walk. As the skin billows out in irregular folds, secondary infection is common wherever the skin is traumatised.

Brugia malayi infection is similar to Bancroftian filariasis described above, with some clinical differences. Elephantiasis is generally confined to the lower extremities, usually to the legs below the knees. It generally does not progress to the woody induration seen in Bancroftian filariasis but remains as a soft pitting edema. Involvement of the scrotum or breast and hydrocele formation are rare in Brugian filariasis.

Occult filariasis may develop in a small proportion of individuals residing in an endemic area. It is characterised by the absence of classical clinical features and of microfilariae in the blood, but with the presence of the parasites in the tissues. Tropical pulmonary eosinophilia is the classical example of occult filariasis. The disorder affects adults, with males being affected twice as often as females. The syndrome is characterised by a nocturnal paroxysmal cough, a low grade fever, weight loss, dyspnea, chest pain, wheezing and scanty sputum production. Extrapulmonary manifestations are poly-arthralgia, and rashes.

Diagnosis The diagnosis of filariasis can be confirmed by the demonstration of microfilariae in blood, hydrocele or chyluria specimens. Nocturnal periodic species are best identified by blood film examination (wet film or giemsa-stained) obtained between 22 00 to 04 00 hours for the presence of microfilaria. For the subperiodic species, the best timefor obtaining a diagnostic blood film is 16 00 hours. Micropore filtration techniques are available at select laboratories for concentrating microfilaria in body species for diagnostic purposes. Antifilaria IgG antibodies can be demonstrated by complement fixation tests or by ELISA.

Treatment Diethylcarbamazine citrate (DEC) is the drug of choice for treating lymphatic filariasis. DEC causes a rapid disappearance of microfilariae from the circulation, though a complete clearing of microfilariae may not be achieved in all people. DEC also has a considerable macrofilaricidal[1] action, though the mechanism of action is obscure. DEC decreases the incidence and prevalence of lymphadenitis, lymphangitis and also reduces the frequency of attacks of funiculitis and epididymitis. The likelihood of developing chronic obstructive lesions is diminished when DEC is administered for an acute attack of lymphangitis. Patients with transient lymphedema, a small hydrocele, hematuria or chyluria, grade I lymphedema usually respond well to treatment with DEC. Patients with large hydroceles or with grade III lymphedema often do not show any

[1] Killing action on macrofilaria (adult worms)

improvement with DEC. DEC is also the drug of choice for tropical pulmonary eosinophilia.

The usual dose of DEC for Bancroftian filariasis is 6 mg/kg of body weight per day orally (preferably in divided doses after meals) for 12 days. The recommended oral daily dose is 3–6 mg/kg of body weight (upto a total of 36–72 mg/kg of body weight) for Brugian filariasis and 6 mg/kg of body weight for tropical pulmonary eosinophilia. The recommended doses will clear the microfilariae in most patients, though repeated courses of treatment may be required for complete parasitic cure. DEC is cheap, safe and tolerated well by most patients. Side effects may be related to pharmacological toxicity (nausea, dizziness, abdominal pain), or due to the filaricidal action (immune reaction to distintegrating micro- and macrofilariae). The latter reactions may be systemic (headache, arthralgia, breathing difficulty) or local (lymphadenitis, transient hydrocele or lymphedema).

Recent studies have revealed that mass treatment of everyone in a community in an endemic area with a single yearly dose of 3–6 mg/kg of body weight can reduce macrofilaria density by 80–90 per cent.

The use of common salt medicated with 1–4 g of DEC per kg of salt has been shown to be very effective in reducing both microfilaremia and clinical disease.

Ivermectin, a semisynthetic macrolide antibiotic with a broad-spectrum antihelminthic action, is an alternative to DEC. A single oral dose of 20–400 μg/kg of body weight is effective in completely clearing blood off microfilariae of W. bancrofti within weeks and is comparable in efficacy to DEC. The response of Brugian filariasis to ivermectin is less dramatic and only a reduction of microfilariae to 15.20 per cent of initial levels is achieved after 4 weeks (Table 8.35).

Oral treatment with coumarin of patients with Bancroftian filariasis has been shown to reduce the edema and complications of elephantiasis. Surgical techniques for elephantiasis now centre around lymphovenous or lymph nodovenous shunts (to improve lymphatic drainage) along with removal of excess fatty and fibrous tissues from the affected extremities.

Acute lymphangitis is treated with anti-inflammatory drugs. Since secondary bacterial infection is common in the presence of preexistent elephantiasis, a course of antibiotics (usually of the penicillin group) may be appropriate in this situation.

Dracunculiasis (Guinea Worm Infection)

Dracunculiasis is an infection caused by Dracunculus medinensis, the largest known nematode which infects humans.

Table 8.35 Drug treatment of filariasis (recommended regimen)

Drug	*Adult dosage*	*Comments*
Diethylcarbamazine	Day 1 : 50 mg oral after meals	• For patients with no microfilariae in blood or skin, a full dose can be given from day 1
	Day 2 : 50 mg tid	
	Day 3 : 100 mg tid	
	Day 4–21 2 mg/kg tid	• Antihistamines or corticosteroids may be required to decrease allergic reactions
Ivermectin	Single dose 20–200 μg/kg	Single dose effective for treatment of microfilaremia

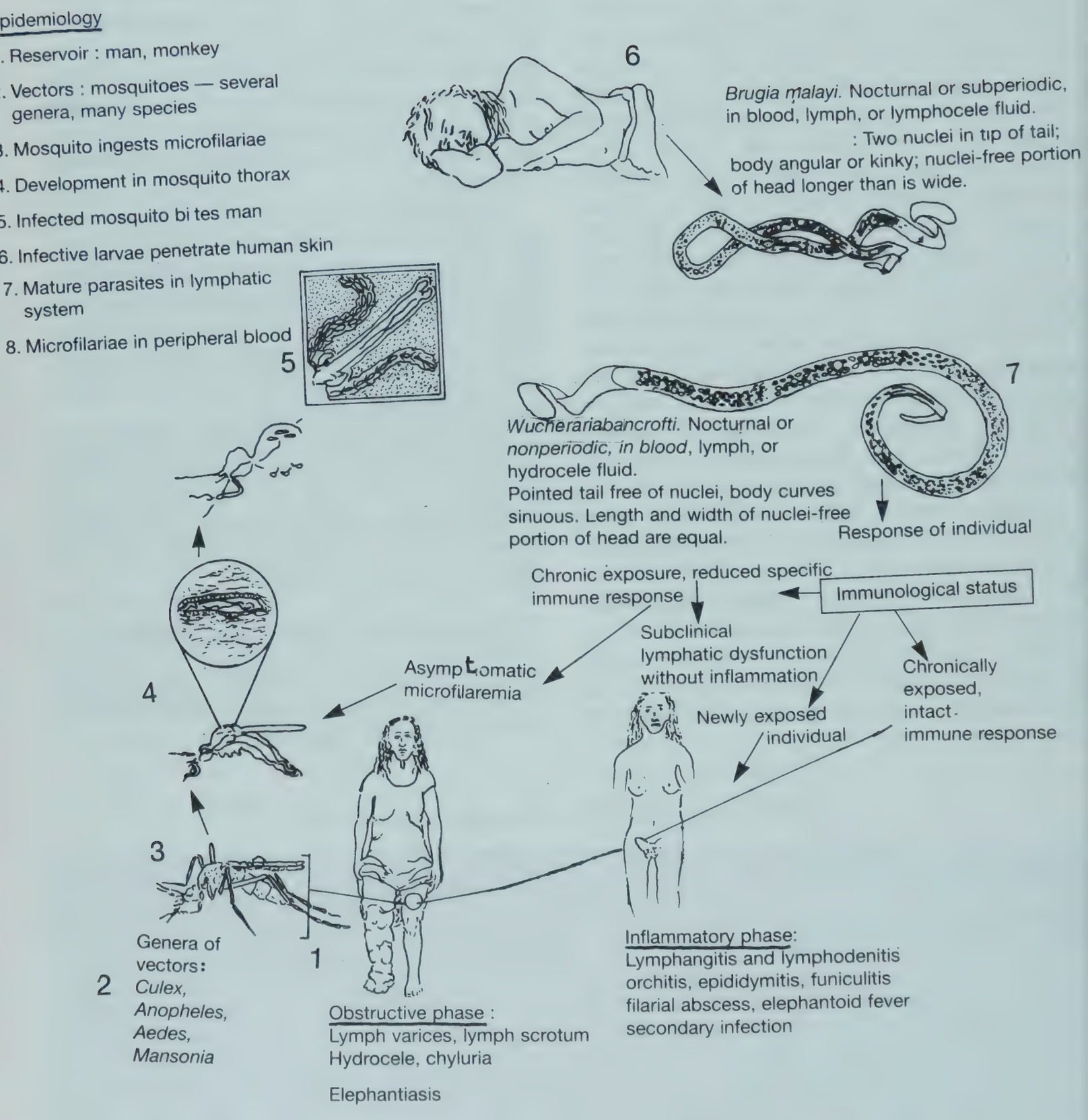

Fig 8.16 Manifestations of filariasis in relation to the life cycle of the filarial worm

Etiology and life cycle The clinical effects of the guinea worm are produced solely by the female worms. The female worm on the surface of host skin liberates thousands of larvae into water, when the infected host skin comes in contact with water. The larvae are ingested by the crustacean cyclops, the intermediate host, and the human host is reinfected by swallowing water containing the infected cyclops. The larvae are released in the stomach of the host, penetrate the intestinal wall, migrate through the lymphatics, mature and reach the subcutaneous connective tissue (most commonly of the legs and feet). The male and female worms mate here after about 3 months and the male worms then die in the tissues. The fertilised female forces itself from the subcutaneous tissue into the skin, where a painful blister appears. When the affected part comes in contact with water, the blister bursts and the female worm protrudes through the skin and expels thousands of larvae into the water. The worm dies after releasing the larvae.

Epidemiology Guinea worm infection afflicts adults (age group 15–45 years) more than children. Rural farmers are particularly at risk because they may drink large amounts of water from infected ponds. The stagnant water in large step wells in India provides an ideal condition for the breeding of cyclops and for the contamination of water by larvae.

It is estimated that there may be six million people infected with guinea worm in India. The disease is widely prevalent in the states of Andhra Pradesh, Gujarat, Maharashtra, Tamil Nadu, Uttar Pradesh, Madhya Pradesh and Rajasthan.

Clinical features The incubation period for guinea worm infection ranges from 10 to 14 months. Symptoms begin just before the worm emerges from the subcutaneous tissues. About a third of patients can feel the worm beneath the skin at this stage. About half the patients may manifest systemic allergic symptoms such as erythema, urticarial rash, suborbital edema or diarrhea. The first physical sign is a 2–5 cm reddish papule with a vesicular centre and indurated margin. The papule soon becomes a blister. The blister ruptures leaving behind a superficial ulcer over the next 3 to 5 days. The majority of skin lesions are on the lower extremities, particularly on the feet and the ankles. The extremity may become painful and edematous. Although the worm may protrude through the ulcer on occasion, it is usually not visible. The site of emergence is prone to secondary bacterial infection. Depending on the location of the site, there may be cellulitis, abscess formation, synovitis, or epididymo-orchitis. Chronic infection can result in fibrous ankylosis of joints or contractures of tendons. Worms that do not emerge usually die and may be visible as calcific densities in X-rays. They may be palpated as hard subcutaneous cords.

Diagnosis A definitive diagnosis of guinea worm infection requires demonstration of an emerging adult worm or the presence of larvae (on microscopic examination of blister fluid). Serologic tests are not helpful.

Treatment The traditional method of treating guinea worm infection has consisted of winding each emerging worm onto a small stick, a few centimetres a day. The ulcer should be kept clean with sterile dressings to prevent secondary infection. Surgical removal of non-emergent worms can also be attempted by incising the skin over the palpable outline of the worm.

Medical treatment with benzimidazole compounds provides symptomatic relief and facilitates the surgical removal of the female worms. Metronidazole (400 mg daily for 10 to 20 days), thiabendazole (50 mg/kg daily for 3 days) or mebendazole (400 to 800 mg daily for 6 days) are equally effective. These compounds, however, do not have any effect on larvae or on non-emergent worms.

Prevention Health education, provision of improved sources of drinking water, filtration or chemical treatment of drinking water sources can significantly reduce the burden of disease. Replacing step wells with protected bore holes and tube wells, raising the edges and building concrete barriers for draw wells (thereby eliminating patient contact with water) are additional measures. The WHO Expert Committee on pesticides has recommended temephos (Abate) for controlling cyclops in water sources.

CESTODE INFECTIONS

Adult Tapeworm Infections

Tapeworms are flat worms which consist of a head (scolex), a neck, and a chain of individual segments called proglottids. Eggs form in mature proglottids. The adult worm attaches with its scolex to the mucosa of the upper part of the small intestine.

Epidemiology Six tapeworms are known to infect humans; three are large (*Taenia solium, Taenia saginata and Diphyllobothrium latum*) and three are small (*Hymenolepsis nana, Hymenolepsis dimunita and Diphylydium caninum*). The fish tapeworm (*Diphyllobothrium latum*) is principally found in the subarctic regions and in Scandinavian countries. The beef tapeworm (*Taenia saginata*) infection occurs in central Asia and central and east Africa. The tapeworm infection encountered in India is due to the pork tapeworm (*Taenia solium*). Humans are the definitive hosts for adult tapeworm infections (taeniasis). They are infected by eating under-cooked or raw meat containing the larval forms of the tapeworms.

Clinical features Large tapeworm infections are usually asymptomatic. On occasion, the adult worm may cause abdominal pain and diarrhea. Rarely, the adult worms may cause obstruction of the hepatobiliary or pancreatic ducts, or appendicitis.

Fish tapeworm infection is associated with macrocytic megaloblastic anemia (see Chapter 15). Infection by small tapeworms is usually asymptomatic.

Diagnosis Tapeworm infection may be diagnosed when the adult worm is passed in the stools. Eggs are found in the stools in 50 per cent of infected patients. A more reliable test is the *perianal cellophane tape* test that can detect eggs in upto 75 per cent of infected subjects.

Treatment and prevention Adult taeniae infection is treated successfully with a single dose of four tablets (2 grams) of niclosamide. The patient is instructed to chew the tablets thoroughly in the morning on an empty stomach. Praziquantel (10 mg/kg) in a single dose is a highly effective alternative. A laxative may be given two hours after the treatment to rapidly eliminate disintegrating segments from the intestines.

Because human beings are the only definitive hosts, the disease can be eradicated with the help of proper education. Cysticerci can be killed by proper cooking of pork (upto 50°C) or by freezing the meat (to –20°C). Meat inspection is an insensitive method for detecting infected meat. Indiscriminate open defecation must be discouraged as this allows pigs access to infected human feces, thus permitting the initiation of another parasitic cycle.

Infection by Larval Forms of Tapeworms

Cysticercosis

Cysticercosis is the infection of humans by the larval stage (cysticercus) of the pork tapeworm (*Taenia solium*).

Epidemiology, pathogenesis and pathology Cysticercosis occurs in areas where human fecal sanitation is poor. It is endemic in Latin America and focally distributed in Russia, India and south-east Asia. If fecally contaminated vegetables are eaten, taenia eggs enter the gut

Table 8.36 Manifestations of cysticercosis

Location	*Pathology*	*Manifestation*
1. Neurocysticercosis (60%)		
a. Parenchymal cysts (majority), seen at grey-matter-white-matter junction	focal inflammation mass effects	epilepsy (focal motor/sensory or generalised), focal deficits intracranial hypertension (headache, vomiting, visual loss and papilledema), dementia, and coma
b. Meningeal cysts (<50%)	adhesive arachnoiditis, arterial thrombosis	obstructive hydrocephalus, cranial nerve dysfunction (especially the optic nerve), intracranial hypertension, vascular events (stroke)
c. Ventricular cysts (15%)	obstruction of cerebrospinal fluid path	increased intracranial pressure, hydrocephalus*
d. Spinal cord cysts (3%)	arachnoiditis, mass effect	spinal meningitis, radiculopathy, neurologic deficits similar to that due to a spinal cord tumour
2. Ocular cysticercosis (3%)	iridocyclitis, chorioretinitis, retinal detachment, disc hemorrhage and edema	periorbital pain, scotomata, deterioration of visual acuity, nodule in eyelid or lacrimal gland
3. Subcutaneous and muscular cysticercosis (5%)	none	palpable nodules, calcific radiologic densities

* Ventricular cysts are most common in the fourth ventricle and may be free floating when they can cause intermittent obstruction presenting as episodic headache with ataxia

nd man becomes the intermediate host. Taenia ggs can also be spread from feces to food by oprophagic flies. Humans can also act as ntermediate hosts by autoinfection or due to egurgitation of gravid proglottids from the ntestines into the stomach (where egg hatching ommences). The ingested egg spawns an mbryo (*hexacanth larva*) that penetrates the ut and disseminates in the bloodstream to levelop into a cystic larva (cysticercus) at any ody site. The sites of predilection are (in order f frequency) the central nervous system, the triated muscles, subcutaneous tissues, the lobe of the eye and the heart. The cysticerci omplete their development in about hree months after entry into the host and usually do not elicit any inflammatory reaction.[1] Symptoms at this stage, if any, are related to a 'mass effect' of the cysts. When the cysts die, they provoke an inflammatory reaction. This is associated with vesicular enlargement, pericyst edema and a vasculitis. Microscopically, there is perivascular cuffing with lymphocytes and plasma cells, while eosinophils and neutrophils surround the cysticerci. Eventually, the cyst degenerates and dies and is surrounded by a dense fibrous capsule which subsequently calcifies. Surrounding the capsule is a narrow zone of granulation tissue. The definitive diagnosis of

[1] Live cysticerci have the ability to coat themselves with host antigens, thereby escaping immune surveillance.

cysticercosis on histology requires identification of an intact cysticercus. On cross-section, there is an outer eosinophilic tegument, a central muscle layer and an inner mesenchyme. The scolex, with two rows of hooklets, is seen within the cyst.

Clinical features Young and middle-aged adults are most commonly afflicted with the disease. The clinical features depend on the tissue of localisation and Table 8.36 depicts the findings associated with the three common forms of the disease. Neurocysticercosis is due to cysts present singly or in large numbers in the brain parenchyma or the meninges. Occasionally, the cysts take on a *racemose* appearance and grow in grape-like clusters in the subarachnoid space. The racemose form is rare in India but is common in the Mexican form of the disease. Ocular cysticercosis usually takes the form of a single, free-floating cyst in the vitreous humour; however, it can be more severe and can result in blindness. The subcutaneous and intramuscular cysticerci are usually asymptomatic. It has been stated that the presence of cutaneous cysticerci strongly suggests involvement of the central nervous system, although the converse is not true. A careful search for pea-sized subcutaneous nodules must be made in every patient with suspected cysticercosis as these nodules can be excised for parasite identification, but the absence of subcutaneous nodules does not exclude cysticercosis.

Cysticerci may be asymptomatic and this is probably the most common 'clinical' syndrome.

Investigations A definitive diagnosis of cysticercosis requires pathologic confirmation in excised tissues. A presumptive diagnosis of cysticercosis can be made based on the characteristic appearance of cysts on imaging and with the help of serologic tests. Peripheral blood eosinophilia is inconstant, being seen in only about 20 per cent. Plain radiographs of the soft tissues may detect multiple, oval or linear, calcified lesions in the muscles and in the subcutaneous tissues. Plain X-ray films of the skull may demonstrate foci of intracranial calcification; elliptiform calcification with a central calcified area (scolex) surrounded by a calcific rim (cyst wall) is pathognomic. CT or MRI scans are the most useful procedures for the diagnosis of neurocysticercosis. A plain CT scan is obtained followed by a contrast-enhanced scan. Viable cysts (vesicular cysts) are rounded areas of low density without contrast enhancement. Dying cysts (colloidal cysts) appear as hypodense or isodense lesions with ring-like enhancement (host inflammation). Dead cysts appear as calcific areas. A combination of CT images may be used since cysticerci in different stages of development may coexist. Contrast enhancement is necessary to visualise ventricular cysts as cysticerci may have the same absorption values as cerebrospinal fluid. On an MRI scan viable parenchymal cysts display CSF intensity on both T1- and T2-weighted images, while degenerating parenchymal cysts show T1 hyperintensity. Calcified cysts, however, are seen more clearly in a CT scan as compared to an MRI scan. Meningeal cysticercosis is seen as meningeal enhancement on contrast-enhanced CT or gadolinium-enhanced MRI. Spinal cysticercosis is evaluated by CT myelography or MRI of the spine. The cerebrospinal fluid may show increased protein, decreased glucose and a cellular mononuclear response; the finding of over 20 per cent eosinophils strongly points to the likelihood of neurocysticercosis.

The two serologic tests which are most useful are the *immunoelectrotransfer blot* test and the ELISA test. The immunoblot test is more sensitive and can be performed on the serum or the cerebrospinal fluid. These tests, however, are not diagnostic and are not routinely available.

The differential diagnosis includes other parasitic neurologic diseases such as tuberculosis, echinococcosis, fungal infections, and neurosarcoidosis. None of these diseases is associated with subcutaneous nodules.

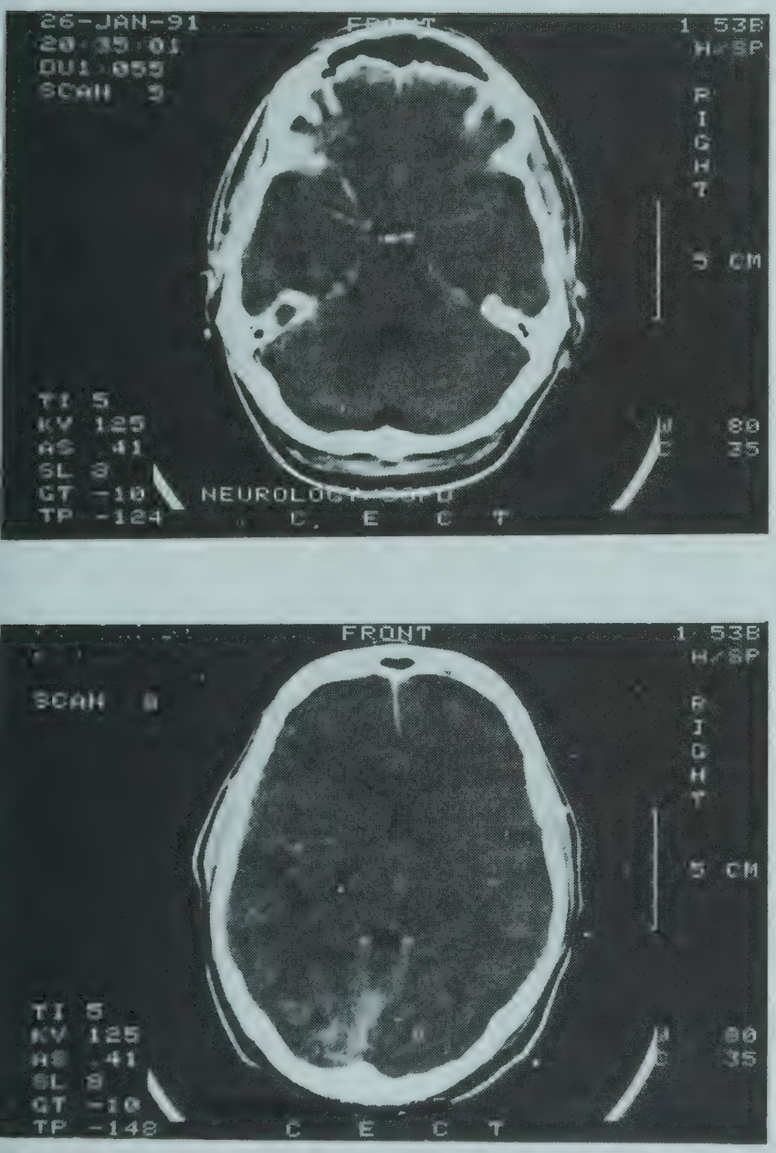

Fig 8.17 The upper part of the CT scan shows contrast enhancement of the subarachnoid spaces. This appearance suggests chronic meningeal inflammation—tubercular, fungal or due to cysticercosis. The lower scan (another slice in the same patient) shows the multiple small enhancing lesions of cysticercosis.

Treatment Treatment of cysticercosis depends on the number of lesions, the organ involved, presence or absence of inflammation surrounding the cysts, and the presence or absence of symptoms in the patient. Patients with only calcified cysts do not require any treatment. It is not clear whether asymptomatic non-calcific neurocysticercosis should be treated since such lesions have a non-progressive course. Single uninflamed lesions can certainly be left alone if the patient is asymptomatic. Acutely inflamed, single parenchymal cysts are known to involute rapidly (over 10 to 12 weeks) and require no treatment. Multiple uninflamed cysts require anthelminthic treatment, especially when symptoms are present. In general, medical treatment is preferable to surgical treatment for cysticercosis. An important exception is ocular cysticercosis which requires surgical removal of the cysts; medical treatment is ineffective and, in fact, contraindicated as death of the cyst could result in an ocular inflammatory response and blindness. In any patient presenting with neurocysticercosis, concomitant ocular involvement must be ruled out by fundus examination combined with orbital CT, orbital ultrasound or an X-ray of skull before drug treatment is initiated.

Praziquantel (50 mg/kg/day for 15 days) and albendazole (15 mg/kg/day for 8 days) in divided doses are effective drugs, with cure rates of over 50 per cent. Albendazole is less expensive, achieves better penetration of the cerebrospinal fluid and is needed for a shorter duration. Anthelminthic drugs may be associated with transient neurologic worsening due to an inflammatory reaction to dying parasites in 15–30 per cent of patients; this may take the form of headaches, meningismus, vomiting or even convulsions. Steroids (oral prednisone, 30 mg/day), therefore, are often combined with drug treatment to diminish this host inflammatory response. Steroids may be started 1–2 days prior to use of the drugs and continued for two weeks thereafter. Dexamethasone, and

to a lesser extent prednisone, may decrease praziquantel bioavailability by 50 per cent. Among the living cysts, parenchymal cysts respond better than intraventricular or sub-arachnoid cysts. Intraventricular cysts and hydroceophalus may require surgical intervention.

Supportive therapy for symptoms such as seizures must proceed in tandem with specific antiparasitic treatment. Calcified (dead) cysts do not respond to treatment. The appropriate index for judging the response to treatment is the clinical symptomatology. If a repeat CT scan is planned to assess the response to drug therapy, this is best done 3 months after a course of treatment.

Prevention Prevention of cysticercosis requires good personal hygiene (washing hands after defecation) as well as avoiding the ingestion of unwashed, uncooked foods such as fruits and fresh vegetable salads.

Echinococcosis

Echinococcosis is the infection of humans by one of three *Echinococcus* species: *Echinococcus granulosus* (cystic hydatid disease), *Echinococcus multilocularis* (alveolar hydatid disease) and *Echinococcus vogeli* (polycystic hydatid disease). Only *Echinococcus granulosus* infection is discussed here as it is endemic in the Indian subcontinent. Alveolar hydatid disease occurs in Central Europe and Siberia and polycystic hydatid disease is encountered in South America and Panama.

Epidemiology Carnivorous mammals such as dogs (*pastoral strain* of parasite) or wolves (*sylvatic strain*) are the primary hosts. The eggs are usually passed in the feces by the primary host who harbours the adult tapeworm in the small intestine. The secondary hosts are usually herbivorous mammals such as sheep that accidentally ingest the feces of the primary host. The primary host is reinfected when it feeds on the tissues of these secondary hosts; the protoscolices within the hydatid cysts in the internal organs are pathogenic to the carnivores that feed on them.

Humans acquire hydatid disease by ingesting food contaminated with eggs of *Echinococcus granulosus*; they are accidental secondary hosts. Human infection occurs primarily in rural areas where dogs are used to manage flocks and where they have access to sheep carcasses. Intimate contact with dogs and poor hygienic conditions are conducive to hydatid cyst infection.

Pathogenesis and clinical features When humans accidentally ingest viable eggs, six-hooked embryos are liberated in the gut lumen; these oncospheres penetrate the intestinal mucosa and enter the portal system. About 65 per cent remain localised to the hepatic parenchyma and develop into unilocular cysts. The remainder are carried in the bloodstream to the lungs (25%), and other organs (muscles 5%, bones 3%, renal 2% and spleen and brain 1% each). Pulmonary involvement is especially more common (than hepatic involvement) in children. Each cyst consists of an outer layer produced by host inflammatory response, a middle laminated chitinous layer (ectocyst) and an inner layer consisting of germinal elements which participates in the generation of daughter cysts (endocyst).

Hydatid cysts increase in diameter at a rate of about 1 to 5 cm per year. Cysts may, therefore, be asymptomatic for a considerable length of time; symptoms are often reported in middle age. Symptoms due to hydatid cysts are related to their 'space-occupying mass' effect or due to cyst rupture.

Hepatic cysts may present with asymptomatic painless hepatomegaly, which is often non-uniform and restricted to one lobe. A cyst of the left lobe may appear as an epigastric mass. Pressure on the hepatobiliary system can result in obstructive jaundice; secondary bacterial cholangitis may occur. Upward enlargement of a

hepatic cyst can manifest as a 'right pulmonary base pathology': right lower lobe atelectasis and right pleural effusion. Physical examination may reveal a 'cystic' or 'elastic' feel and fluctuation may be elicited. A *hydatid thrill* may be elicited.[1] Rupture of a hepatic cyst results in a dramatic picture and varies with the site of rupture. Allergic manifestations such as urticaria, bronchospasm and edema are common. Intraperitoneal rupture results in signs or peritonitis, pleuropulmonary rupture manifests as pneumothorax of empyema, intrabronchial rupture can result in spasmodic coughing with sputum containing cyst fragments, and biliary rupture can result in biliary colic with jaundice.

Pulmonary cysts are often asymptomatic but can result in hemoptysis, parenchymal compression (segmental atelectasis) or signs of a consolidation. Bone cysts can result in pathological fractures or severe bone pain; the vertebrae are most often affected and neurologic symptoms can occur due to epidural extension of bone cysts with spinal cord compression. Renal cysts produce hematuria, albuminuria, loin pain or a palpable mass simulating a hydronephrosis. Cerebral cysts are rare but are apt to cause early symptoms which range from seizures, signs of increased intracranial pressure to blindness (ocular cysts).

Investigations The diagnosis of hydatid disease is often recognised from the results of radiographic studies. Plain chest X-ray films detect pulmonary cysts which appear as rounded irregular pulmonary masses.[2] Calcification of the wall is uncommon (except in hepatic cysts).

Hepatic cysts are commonly detected on sonography, a CT scan or an MRI scan; the choice of the test is based on availability and expense. Hepatic hydatid cysts appear as well-defined cysts with calcific rims; the presence of daughter cysts that are free within the cyst or are adherent to the inner cyst layer is a pathognomonic sign.

Several serologic tests may be helpful in establishing the diagnosis of echinococcosis but are not freely available and there are doubts regarding their sensitivity and specificity. Two tests that have high sensitivity and acceptable specificity (but poor availability) are the *immunoblot* test and a gel diffusion assay for genus-specific *arc 5*. The *Casoni* skin test is non-specific and is of little diagnostic value.

Till recently, percutaneous aspiration of cyst contents for diagnostic purposes was thought to be contraindicated because of the fear of rupture (with the attendant risk of anaphylactic reactions). Recent reports from select centres have reported safe results provided the procedure is CT- or sonography-guided; the aspiration of protoscolices or hydatid membranes is diagnostic.

Treatment The definitive therapy for E. granulosus cysts is surgical excision. During surgery, special care is taken to avoid spilling the cyst contents; spillage can result in anaphylaxis and dissemination of infection. Some authorities recommend medical treatment with albendazole 2 weeks before and for 2 weeks after surgical treatment to prevent such dissemination. Before excision, the cyst may be aspirated and scolicidal solutions (0.1% cetrimide, ethanol, 0.5% silver nitrate, or hypertonic [20%] saline) are instilled.

Medical treatment of hydatid disease has emerged as an interesting alternative. Studies from Kenya have revealed promising results with albendazole as the initial treatment of hydatid disease of the liver, lung and bones. Albendazole is administered at a dose of

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[1] This sign is rarely elicited. On sharp pressure with fingers, a momentary thrill (like a 'quivering jelly') may be palpated. It is probably related to the impact of daughter cysts against the tense, elastic cyst wall.

[2] Occasionally, the cyst wall may separate into its layers and air may leak into the intervening space; this appears on plain films as the 'meniscus, double arch, or water lily' sign.

15 mg/kg/day (usually 4 tablets [800 mg] per day) for 8 weeks; 2 courses, each of about 4 weeks duration, separated by a rest period of 2 weeks havealso been used. Medical treatment must be monitored with repeat sonographic, CT or MRI studies. About a third of cases are cured, another third show improvement, and the third show no change. If mebendazole is used, the dose is 50 mg/kg/day (in 3 divided doses) for three months.

Prevention Mass treatment of pet dogs (5 mg/kg praziquantel at monthly intervals), control of stray dogs and health education are important preventive measures.

Other helminthic infections arre summarised in Table 8.37.

Table 8.37 Less common helminthic infections

Disease	*Etiology*	*Epidemiology*	*Symptoms*	*Diagnostic tests*	*Treatment*
Infection due to nematodes					
Trichinosis	Trichinella spiralis	acquired by eating infected/ raw pork	fever, myalgias, periorbital edema, diarrhea, splinter hemorrhages	biopsy of skeletal muscle near tendon attachment; positive intradermal test (Bachman test)	**Intestinal:** Thiabendazole 22 mg/kg bid p.o. x 5 days **Muscle:** Mebendazole 300 mg tid p.o. x 3 d, followed by 500 mg tid+ x 10 d Prednisolone 40–60 mg/d p.o. x 3–5d, then taper
Trichuriasis (Whip worm)	Trichuris trichura	eggs are present in fecally contaminated vegetables/food	usually asymptomatic; abdominal pain, diarrhea on occasion	eggs are found in feces	Mebendazole 100 mg bid p.o. x 3 d or Albendazole 400 mg po (single dose)
Strongyloidiasis	Strongyloides stercoralis	filariform larvae present in soil penetrate skin of feet, migration via lungs, intestines	dermatitis, cough, epigastric pain, diarrhea	demonstration of rhabditiform or filariform larvae	Thiabendazole 22 mg/kg bid p.o. x 2 days or Albendazole 400 mg p.o. x 3 days
Loiasis	Loa loa	mangrove fly, Chrysops, transmits microfilariae	worm migrates through the skin resulting in transient swellings of the trunk and extremities–*Calabar* nodules; fever, urticaria, bulbar conjunctival redness	microfilariae identified in thick smears, eosinophilia	Diethylcarbamazine Day 1: 50 mg p.o. Day 2: 50 mg tid Day 3: 100 mg tid Day 4–21: 2 mg/kg tid

Table 8.37 Less common helminthic infections (contd.)

Disease	*Etiology*	*Epidemiology*	*Symptoms*	*Diagnostic tests*	*Treatment*
Onchocerciasis (River blindness)	Onchocerca volvulus	female black fly (*Simulium*) transmits microfilariae	microfilariae migrate causing itch, rash and reach the eyes; may cause blindness	microfilariae in skin, urine	Ivermectin 150 μg/kg p.o. repeated every 6 months
Visceral larva migrans	Toxocara canis	eggs are in soil; infected barefoot children	hepatomegaly, fever, pneumonitis, neurologic symptoms	larvae in liver biopsy	Diethylcarbamazine 2 mg/kg tid p.o. X 10 days or Thiabendazole 22 mg/kg bid p.o. x 5 days
Cutaneous larva migrans	Ancylostoma braziliense	eggs in sandy soil, sea bathers	larvae cause serpiginous track subcutaneously	none, unless larvae are isolated from the soil	Thiabendazole 22 mg/kg bid p.o. x 5 days
Gnathostomiasis	Gnathostoma spinigerum	acquired by eating improperly cooked fresh water fish	painless, pruritic migratory swellings	identification of larvae in tissues	Surgical removal
Angiostrongyliasis (eosinophilic meningitis)	Angiostrongylus cantonensis	acquired by ingestion of raw or improperly cooked snails, slugs	headache, neck ache, fever	cerebrospinal fluid contains mainly eosinophils	mebendazole 100 mg bid x 5 days
Infection due to flukes					
Paragonimiasis	Paragonimus westermanii	acquired by eating improperly cooked crabs, crayfish	cough and hemoptysis	orange-brown pigmented eggs are found in sputum; chest X-ray may reveal cavities	Praziquantel 25 mg/kg tid p.o. x 2 days

Table 8.37 Less common helminthic infections (contd.)

Disease	*Etiology*	*Epidemiology*	*Symptoms*	*Diagnostic tests*	*Treatment*
Fascioliasis	Fasciola hepatica	acquired by ingestion of infected aquatic vegetables such as watercress	biliary colic, hepatitis	eggs can be detected in stools or in duodenal fluid	Bithionol 20 mg/kg bid p.o. every other day x 14 d
Fasciolopsiasis	Fasciola buski	acquired by eating infected water chestnuts	diarrhea, abdominal pain, intermittent constipation	eggs or flukes in stools	Praziquantel 25 mg/kg tid p.o. x 1–2 days
Clonorchiasis (Chinese liver fluke disease)	Clonorchis sinensis	acquired by eating improperly cooked fish	abdominal pain, hepatic pain, anorexia	eggs can be detected in stools or in duodenal fluid	Praziquantel 25 mg/kg tid p.o. x 2 days
Schistosmiasis	Schistosoma mansoni (intestine, liver), S. hematobium (urinary bladder), S. japonicum	cercariae infect humans exposed to contaminated lake water	fever, pruritus, urticaria (Katayama fever); urinary bladder infection: hematuria, urethral bladder, bladder pain, urinary tract obstruction; intestinal infection: diarrhea, dysentery, abdominal pain, portal hypertension	eggs found in stool, urine or biopsy of tissue	Praziquantel 20 mg/kg every 4 hr p.o. x 2–3 days, steroids for fever

KEY CONCEPTS

Intestinal nematodes

Hookworm

- Two species, *Necator americanus* and *Ancylostoma duodenale* commonly cause the disease.
- The infection is most common in warm tropical areas where night soil is used as manure and people walk barefoot. It is one of the most common causes of iron deficiency anemia in India.
- The larval forms penetrate the skin of the feet (cause *ground itch*), then enter the bloodstream and reach the lungs; they then migrate up the tracheobronchial tree and are swallowed into the intestine where they mature into adults and suck blood.
- *Iron deficiency anemia* is the most common manifestation; sequelae of anemia may be evident. Pulmonary symptoms (wheezing, cough) may occur during larval migration.
- The diagnosis is by demonstrating hookworm ova in stools.
- The treatment is with dietary iron supplementation, and pyrantel pamoate or mebendazole.

Roundworm

- *Ascaris lumbricoides* infection is endemic in tropical areas where there is indiscriminate open air defecation; transmission is by the feco-oral route.
- The ingested eggs develop into larvae in the intestine. The larvae then penetrate the intestinal wall and enter the blood stream. From the bloodstream they reach the pulmonary alveoli, migrate up the tracheobronchial tree and are then swallowed back into the intestine.
- Fever, cough and wheezing may occur during transpulmonary migration. Intestinal worms can cause abdominal pain. Rarely, the worms can cause intestinal obstruction or appendicitis.
- The diagnosis is by demonstrating ova in the stools or by examining a worm passed in the stools.
- The treatment is with mebendazole/pyrantel pamoate.

Pinworm

- *Enterobius vermicularis* is one of the most common helminthic infections in children; transmission is by feco-oral spread or autoinfection.
- Perianal pruritus is caused by the gravid female's laying sticky eggs in the perianal region at night; vaginitis may occur in girls.
- A *scotch tape test* is useful for demonstrating perianal eggs.
- The treatment is with a single dose of mebendazole/pyrantel pamoate

Tissue nematodes

Filariasis

- *W. bancrofti* and *B. malayi* are tissue nematodes which cause filariasis. Mosquitoes are the vectors (aedes, culex, mansonia species) and transmit infective microfilaria. The disease is endemic in the tropics.
- The clinical features include *asymptomatic microfilaremia* (endemic areas), *filarial fever* and *acute lymphangitis* with lymphadenitis. *Chronic lymphatic fibrosis* results in elephantiasis, hydrocele and chyluria.
- The diagnosis is by demonstrating microfilariae in peripheral blood smear or in hydrocele fluid (concentration technique).
- The treatment is with diethylcarbamazine (21 days); surgery may be necessary for complications such as elephantiasis and hydrocele.
- Mass prophylaxis with DEC (as such, or added to common salt) is suggested as a preventive measure in the community.

Guinea worm

- This is caused by the tissue nematode *Dracunculus medinensis;* cyclops is the vector.
- It is the disease of subcutaneous tissues acquired typically by *drinking contaminated water* from *step wells.* The ingested larvae migrate through the gut wall, reach and mature in the retroperitoneum; from there the adults migrate into the subcutaneous tissues. An intense local reaction ensues which is followed by ulceration of the overlying skin (often at the ankles).
- The diagnosis is by examining a *skin blister* with the worm at the base; the worm reflexly discharges larvae into water on contact.
- Treatment traditionally consists of winding the worm on a stick; surgical removal often fails. Metronidazole reduces local reaction.

Cestodes

Cysticercosis

- The infection is caused by the larval form of the pork tapeworm, *Taenia solium.* Humans get infected by ingesting eggs or by autoinfection. The *hexacanth* embryos penetrate the intestinal wall and are carried to the subcutaneous tissues, CNS, muscles and viscera where they develop into *cysticerci.* Viable cysticerci elicit a mild inflammatory reponse, while dead ones provoke an intense reaction.

- The clinical features include muscle pains, and palpable subcutaneous or intramuscular nodules. CNS involvement (*neurocysticercosis*) may lead to varied manifestations based on the location and the size of the cyst. These include meningoencephalitis, chronic basilar meningitis (*racemose appearance*), hydrocephalus and seizures.
- Cystic lesions in the brain are best visualised by a CT scan or an MRI. The *Immunoblot* test is a serologic test. Muscular and subcutaneous cysts may appear calcific on an X-ray. Tissue diagnosis can be obtained with a biopsy.
- Praziquantel (15 days) is the drug of choice; albendazole (8 days) is equally effective. Steroids are necessary as adjunctive therapy for CNS disease (to prevent cerebral edema which can be provoked by larval death). Surgical treatment is preferred for ocular cysts.

Echinococcosis

- The infection is by *Echinococcus granulosus*. Humans is the *intermediate* host are whereas dogs are the definitive hosts.
- The liver and lungs are most often affected. Hepatic cysts manifest with: RUQ abdominal mass, abdominal pain and biliary compression with cholestatic jaundice. Lung cysts give rise to hemoptysis, cough, chest pain or anaphylaxis (associated with intrabronchial rupture).
- The CT scan appearance is characteristic: daughter cysts within larger cysts and *egg-shell calcification. Arc 5* on immunoelectrophoresis has high specificity.
- Surgical excision is the treatment of choice when feasible. Medical treatment with mebendazole/ albendazole cures a third and produces symptomatic improvement in the rest.

8.11 Fungal infections

Fungi are single cell organisms with a nuclear membrane and a rigid cell wall (like plants) but lack chlorophyll and show little cellular specialisation. Fungi may occur as *yeasts* (single cell oval-shaped forms) or as *moulds* (organisms with hyphae or branching filaments) depending on the environment. Some fungi can occur in both forms (*dimorphic*). Fungi are generally organisms of low virulence and seldom produce extracellular toxins. Fungal diseases are called *mycoses.* Human to human transmission is rare in fungal infections. Fungal infections can be classified into four categories:

1. *Superficial* fungal infections are due to keratinophilic fungi that can infect the stratum corneum of skin, hair and nails. These organisms are broadly termed *dermatophytes.* The common infections due to this group of organisms are listed in Table 8.38. These infections are acquired by direct contact.
2. *Subcutaneous* fungal infections are a group of infections acquired by inoculation and are confined to the subcutaneous tissues. Lymphatics, bones and joints may be involved secondarily. Mycetoma is a prototype of this group and is discussed in detail below. Less common infections in this group are summarised in Table 8.39.
3. The *deep mycoses* are a group of infections that are acquired principally through the respiratory route by inhalation. Cryptococcosis is an example and is discussed in the section on infections of the nervous system. Other systemic mycoses are tabulated in Table 8.40.
4. *Opportunistic* infections are a group of fungal infections seen especially in immunocompromised hosts. These fungi may also exist as normal body flora in the healthy subject. Candidiasis is an example of this group.

Mycetoma (Madura foot, Maduromycosis[1])

Mycetoma is a chronic, localised, slowly progressive subcutaneous infection characterised by granuloma formation and suppuration.

Etiology Mycetoma is not always due to fungal infection. In fact the commonest causes of mycetoma (about 60%) are bacteria belonging to the actinomycetes group (*A. madurae, N. brasiliensis*– hence called actinomycetoma). The fungal causes of mycetoma (40%) include *Madurella mycetomatis, M. grisea* and *Pseudoalles-cheria boydii,* (called eumycetoma).

Epidemiology Mycetoma is endemic in tropical countries like India. Areas of endemicity are characterised by the presence of thorny bushes and a climate where the rainy season with high humidity alternates with a relatively hot dry season. The disease is more common in young adults and in those who walk barefoot and are exposed to infected soil and

[1] The disease was initially reported from Madurai district in Tamil Nadu 140 years ago.

Table 8.38 Common dermatophytoses and their treatment

Infection (site)	*Organism*	*Antimicrobial agent*		*Adjunctive measures and comment*
		Primary	***Alternative***	
Tinea pedis* (toe webs, skin of feet)	Trichophyton rubrum, Trichophyton mentagrophytes Epidermophyton floccosum	Topical miconazole, clotrimazole, ciclopiroxolamine twice daily for 2–3 weeks	Undecylenic acid or tolnaftate or haloprogin	Keep toe spaces dry and separated
Tinea cruris (groin)	E. floccosum, T. rubrum, T. mentagrophytes	Topical imidazoles as above	Ketoconazole (2%) cream	Avoid tight clothing; keep skin cool and dry; Consider griseofulvin if persistent
Tinea corporis* (body)	T. rubrum, T. mentagrophytes, microsporum canis	Topical imidazole for 4–6 weeks for localised disease	Ketoconazole, oral 200 mg/day for 4 weeks	Follow-up for hepatotoxicity
Tinea unguium* (nails)	T. rubrum, T. mentagrophytes	Griseofulvin oral 500 mg bd for: 3–4 months (finger nails) or 6 months (toe nails)	Terbinafine is a new investigational agent: 125 mg bd for 4 weeks	Relapse rate 50% for toe nails, hence ignore asymptomatic isolated infection in elderly; consider nail avulsion
Tinea capitis (hair on scalp)	M.canis, Microsporum audouini, Trichophyton tonsurans, Trichophyton verrucosum	Grisefulvin, oral 500 mg/day for 4–6 weeks	Ketoconazole, oral 200 mg/day for 4 weeks	Topical imidazoles may be used in addition to oral agents, sterilise/change hair comb
Tinea ** versicolor (skin of trunk)	Pityrosporum orbiculare (formerly Malassezia furfur)	Ketoconazole, oral 400 mg single dose or as a topical 2% cream or 2.5% selenium sulphide lotion (Selsun)	Topical imidazole cream	Apply daily at night for 7 days (Selsun) or 2 weeks (Ketoconazole)

* Tinea pedis is also called athlete's foot, Tinea corporis is called 'dhobi itch', Tinea unguium is called 'onychomycosis'.

** Tinea versicolor is strictly not a 'dermatophyte'.

thorns. Understandably, the lower extremities are affected preferentially.

Pathology and pathogenesis Traumatic inoculation of the fungus into the subcutaneous tissues elicits an inflammatory response characterised by granuloma formation. Pathologically, there is dense fibrosis and the presence of cyst-like spaces that contain refractile eosinophilic granules. The inflammation extends into the osseous tissue resulting in osteitis. Bone inflammation may be predominantly osteoclastic (resorption), osteoblastic (bone formation) or mixed (with bone destruction, spicule formation and cavitation).

Clinical features Usually the patient presents with a painless firm subcutaneous plaque that enlarges progressively. Areas of the skin may ulcerate and there may be sinus tracts that discharge granules of various colours (depending on the etiologic agent). Old sinuses may heal and are replaced by new ones. The feet are most often involved (70%), although mycetoma may occur on the buttocks, hands, back or the scalp. Spread of infection occurs along fascial planes but nerves are typically resistant; mycetomas are painless. Secondary infection is uncommon (due to antibacterial substances elaborated by the fungi). The swollen limb can cause considerable disability and work impairment in patients.

Diagnosis A definitive diagnosis of mycetoma can be made by the characteristic tissue findings on histopathology and the species can be identified by examining the granules. The differential diagnosis includes chronic bacterial osteomyelitis.

Treatment The distinction between a bacterial and a fungal mycetoma is very important and of direct therapeutic significance. Medical treatment is effective for bacterial mycetomas and consists of rifampicin (4 mg/kg/day) and streptomycin (14 mg/kg/day i.m.) for the first three months combined with dapsone (1.5 mg/kg bid) or cotrimoxazole for two years (4–24 months).

Eumycetomas are as a rule unresponsive to medical treatment and the management consists of radical surgical removal.

Prognosis The prognosis of actinomycetoma is good if treated early. Eumycetomas have a bad prognosis and a portion of the limb may require amputation.

Prevention The habit of walking with slippers is likely to reduce the burden of disease due to this group of fungi.

Candidiasis

Etiology and epidemiology Candidiasis is a mild superficial fungal infection caused by organisms belonging to the genus Candida. These fungi are part of the normal flora of the gastrointestinal tract, mouth, vagina and skin. Most infections are of endogenous origin; these organisms can proliferate and become infective under certain conditions. The most common predisposing factor is the use of broad-spectrum antibiotics; this is associated with a decrease in the normal flora. Vulvovaginal candidiasis is associated with pregnancy. The organism may be systemically introduced from intravenous sites, or through urinary or other indwelling catheters. Infection is also common when the cellular immune response is impaired: diabetes mellitus, acquired immunodeficiency syndrome, cancer, cytotoxic drug treatment, and drug abuse. Most infections are cause by *Candida albicans* and *Candida tropicalis*. Other less common infective strains include *Candida parapsilosis* (cutaneous infection, endocarditis) and *Candida guillermondii* (endocarditis).

Clinical features Superficial candidiasis affects the skin, nails and oropharyngeal mucosa. Skin lesions take the form of a scaly, erythematous, papular rash typically in the *intertriginous* areas:

Table 8.39 Subcutaneous fungal infections

Disease	*Etiology*	*Epidemiology*	*Symptoms*	*Diagnostic tests*	*Treatment*
Diseases due to subcutaneous fungal infection					
Sporotrichosis	Sporothrix schenki	occupational disease among gardeners, farmers	begins as a nodule after a thorn prick, develops imtoan ulcer with lymphatic involvement, pus formation	culture of pus	Iodides are effective : 0.3 g po tid, or Itraconazole 200 mg/d x 6 months
Rhinosporidiosis	Rhinosporidium seeberi	probably via implantation on non-intact mucosa	polypoid masses on nasal, conjunctival and pharyngeal mucosa	biopsy of the lesion reveals granuloma formation with giant cells surrounding spore-containing sporangia	Amphotericin B, with or without surgery
Chromoblasto-mycosis	Phialophora verrucosa, Cladosporium carrioni	organism penetrates traumatised tissue in contact with soil, vegetation	spreading subcutaneous mycosis of lower extremities with cauliflower-like appearance in advanced lesions	pus culture and smear	Surgical excision or cryosurgery; Itraconazole 100 mg p.o. daily x 18 months

Table 8.40 Uncommon deep mycoses

Disease	*Etiology*	*Epidemiology*	*Symptoms*	*Diagnostic tests*	*Treatment*
Infections due to deep mycoses					
Coccidioido-mycosis	Coccidioides immitis	fungus in soil transmitted by aerosol mode	**Primary:** respiratory infection, flu-like illness with erythema nodosum. **Progressive:** Pulmonary lesions resembling tuberculosis, multiple body abscesses	identification of fungus in smears	**Pulmonary** • Ketoconazole/ Fluconazole/ Itraconazole 400 mg p.o. x 9–12 months. • Amphotericin B 0.6 mg/kg/d i.v. x 7 d, then 0.8 mg/kg/d (total dose 2.5 g) **Meningitis:** Amphotericin B as above i.v. + intrathecal 0.1–0.3 mg/day
North American blastomycosis	Blastomyces dermatitidis	conidia are infective by aerosol route	fever, cough, dyspnea, multiple body abscesses in skin, bone, prostate and scrotum	smear and culture of sputum, serologic tests available	Ketoconazole 200 mg/d p.o. with meals x 6 months
South American blastomycosis	Paracoccidioides brasiliensis	conidia infective by aerosol route	ulceration of nasopharynx, oral-rectal ulcers, skin ulcers, lymphadenopathy	culture of fungus from exudates	Ketoconazole 400 mg/d p.o. x 6–18 months; Amphotericin B is an alternative

Table 8.40 Uncommon deep mycoses (contd.)

Disease	*Etiology*	*Epidemiology*	*Symptoms*	*Diagnostic tests*	*Treatment*
Histoplasmosis	Histoplasma capsulatum	inhalation of spore leads to infection	asymptomatic to severe respiratory symptoms, pulmonary inflitration, hilar adenopathy, fever, hepatosplenomegaly	identification of organisms in cultures or smears of sputum, exudates, bone marrow; calcific densities on X-ray (to be differentiated from tuberculosis which is far more common)	**Pulmonary:** Itraconazole 200 mg/d p.o. x 9 months or Ketoconazole 400 mg/d p.o. x 6 months **Disseminated:** Amphotericin B 50 mg/kg i.v. daily x 2 weeks, followed by same dose on alternate days
Mucormycosis	Mucor, Rhizopus, Absidia	inhalation, ingestion of spores or inoculation of traumatised mucosa, skin; especially in immunosuppressed states	**Pulmonary:** pulmonary infiltrates, infarction **Craniofacial:** nasal and paranasal sinus infection, palatal perforation, cavernous sinus thrombosis. **Gastrointestinal form:** mucosal thrombosis with gangrene of GI tract	cultures alone are not diagnostic because these fungi are widely prevalent	Amphotericin B 0.8 mg/kg/d i.v. (total dose 2.5–3.0 g)

below the breast, in the axillae, groin, and in between toes and fingers. Nail infections are characterised by redness and swelling of the nailbed and purulent discharge from the nail folds. Oropharyngeal candidiasis (*thrush*) appears as cream-coloured or bluish-white patches on the tongue, mouth and pharynx. Esophageal infection presents as dysphagia and retrosternal pain. Vaginal infection presents as a whitish discharge along with pruritus and local excoriation. Systemic infection presents with symptoms referable to the organ affected.

Diagnosis The diagnosis of superficial candidiasis depends on demonstration of *Candida* on a Gram-stain of skin, vaginal or mucosal scrapings prepared in potassium hydroxide solutions. A definitive diagnosis of invasive candidiasis requires the isolation of the organism from tissue cultures or the demonstration of organisms in tissue biopsy specimens.

Treatment Oral candidiasis is treated with oral nystatin or clotrimazole. In immunocompromised patients, ketoconazole (400 mg/day) and flucnaozole (400 mg/day, 1,200 mg/day for 4 weeks) may be effective. Esophageal infection may be treated with high-dose oral nystatin, ketoconazole for 14 days or with low-dose amphotericin B for at least 5 to 7 days. For systemic infections, amphotericin B (0.4 mg/kg/day i.v. for 6 weeks) is the drug of choice.

KEY CONCEPTS

Fungal infections

- *Dermatophytes* are keratinophilic fungi which cause infection of the skin, hair and nails. Several species are recognised; the diagnosis is by examining skin scrapings/hair (KOH preparation). The treatment consists of topical/oral imidazoles.
- *Mycetoma* is a destructive chronic granulomatous subcutaneous infection. It may be fungal (*Madurella mycetomatis:* unresponsive to antibiotics) or bacterial (*Actinomycetes:* responsive to antibiotics) in origin. The skin lesions may discharge variegated granules. The involvement of underlying bones is typical.

Candidiasis

- *Candida* is a ubiquitous commensal which causes infection especially in diabetics and in patients with impaired CMI.
- Infections include intertrigo, vulvovaginitis, thrush, esophagitis, intravascular device colonisation with candidemia, and disseminated infection (in neutropenic patients).
- The diagnosis is by examining skin scrapings and throat swabs for the organism.
- The treatment consists of gentian violet for oral lesions, topical imidazoles for intertriginous lesions, ketoconazole or oral nystatin for esophageal infection, and i.v. amphotericin B for disseminated infection.

8.12 Diseases due to ectoparasites

Pediculosis

Pediculosis refers to the infestation of humans by any one of three bloodsucking lice: *Pediculus humanus var. capitis* (head louse), *Pediculus humanus var. corporis* (body louse), and *Phthirus pubis* (pubic or crab louse).

Epidemiology Pediculosis is associated with conditions of overcrowding, poor sanitation and poor personal hygiene. The most common infestation is pediculosis capitis. The lice may be transmitted directly from person to person or indirectly through contact with contaminated personal objects (such as combs and bedding). Pediculosis pubis is usually transmitted sexually. Lice eggs can live for up to 10 days after treatment and can be a source of relapse.

Clinical features All forms of pediculosis cause intense pruritus. *Pediculosis capitis* is confined to the scalp and is most prevalent in women and children. As examination of the itchy scalp may reveal the lice, and lice eggs (nits), which are white and are attached to the hair shafts. Excoriation of the scalp, sometimes with secondary bacterial infection, may be seen. The posterior cervical glands may become enlarged.

Pediculosis corporis[1] affects areas of the body covered by clothing. Body lice live in the seams of clothing, and they attach to the body only to feed. Characteristic lesions include erythematous macules (with red puncta due to bites) and linear scratch marks on the shoulders, buttocks, and abdomen. Secondary bacterial infection may occur resulting in furunculosis.

Pediculosis pubis occurs in the hairy anogenital region. Blue macules (which are caused by the lice's habit of sucking blood), may be seen on the thighs or pubic area. These lice are especially difficult to spot.

Treatment One per cent lindane applied once a day for two days is very effective for the treatment of pediculosis. For the treatment of pediculosis capitis, lindane shampoo is applied to the scalp, followed by thorough rinsing of the scalp. Adherent nits may be removed with a fine-toothed comb. *A repeat treatment in 7–10 days is advisable because the initial treatment does not kill all the eggs.* Lindane should not be applied to the face and eyelids, because it irritates; eyelash infestation may be treated by local application of 0.25 per cent physostigmine ophthalmic ointment. One per cent permethrin cream rinse or 0.5 per cent malathion lotion are also effective for the treatment of pediculosis. All family members should be carefully examined for pediculosis and treated, if necessary, to avoid reinfection. To prevent the spread of lice, contaminated clothing should be washed in boiling water and items such as combs should be cleaned by soaking in 5% Lysol solution. Antibiotics may be indicated in the presence of secondary bacterial infection of excoriated lesions.

[1] Also called Vagabond's disease

Scabies

Scabies is a skin disease caused by infestation with the itch mite *Sarcoptes scabiei.*

Epidemiology The mite bores into the stratum corneum of the skin, forming superficial burrows in which it deposits its eggs. Scabies is transmitted by skin to skin contact with an infected individual. The ectoparasite does not survive for more than 48 hours away from the skin; spread due to exposure to contaminated bedding or clothing is less common. The scabies mite can also be transmitted by sexual contact.

Clinical features The principal manifestation of scabies is severe itching. Itching tends to be worse at night. The webs of the fingers, the flexor aspects of the wrists, the axillary folds, the lower buttocks, the male genitals, and the breasts of females are typically affected. The characteristic lesions are erythematous papules and vesicles with prominent scratch marks. The burrows of the female Sarcoptes may be seen as irregular wavy lines with a minute papule at one end. The face is usually spared other than in infants (who can develop 'kiss lesions' on the cheeks while breast-feeding). The lesions can undergo secondary bacterial infection. Infected scabies lesions have been associated with episodes of postinfectious glomerulonephritis in the tropics.

Atypical lesions may be seen in patients who are malnourished or immunosuppressed. In these individuals the lesions may be crusted and hyperkeratotic (crusted scabies).

Diagnosis The diagnosis of scabies may be confirmed by scraping the burrow and examining the scrapings under the microscope for the presence of the scabies mite or its eggs.

Treatment The following agents are all effective for the treatment of scabies: 1 per cent lindane (gamma benzene hexachloride) lotion or cream; 20 per cent benzyl benzoate solution; crotamiton cream; and 5 per cent sulphur ointment. The patient is instructed to have a thorough bath and then apply one of the above-mentioned agents over the entire body, excluding the face and scalp. Traditionally, patients are instructed not to have a bath for the next 24 hours; however, an application for six hours has been shown to be just as effective. A second application is usually unnecessary but may be instituted one week later. Family members should be treated to reduce the risk of reinfestation. Crotamiton cream or sulphur ointment are the preferred scabicidal agents for young children and pregnant women. Permethrin (5 per cent) is an alternative agent that is effective in cases of lindane-resistant scabies.

Treatment of infected scabies lesions is started with an appropriate antibiotic initially, followed within a week by the application of any of the scabicidal agents mentioned above. A postscabies itch, which is probably a hypersensitivity reaction, often follows treatment and may persist for several weeks. It can be treated with an antipruritic or corticosteroid cream and must be distinguished from reinfestation.

KEY CONCEPTS

Pediculosis

- ➢ This is the infestation of scalp or pubic hair by lice. Overcrowding and poor personal hygiene predispose to the infection.
- ➢ Pruritic skin lesions in the neck, matting of hair, and posterior cervical lymphadenopathy are seen. Red puncta indicate bite sites on the skin.
- ➢ The diagnosis is by demonstrating nits in the hair or adult lice on scalp or seams of clothing.
- ➢ The treatment is with 1% permethrin or 1% lindane. Hair combs should be cleaned. Recurrences are common.

Scabies

- ➢ The itch mite (*Sarcoptes scabei*) burrows beneath the stratum corneum and produces typical *linear burrows*, acuminate papules and intense pruritus.
- ➢ The itching is worse at night. Lesions typically involve the finger webs, skin folds, and the flexor surfaces but spare the face. Bacterial superinfection may occur.
- ➢ The diagnosis is by demonstrating the mite in burrow scrapings.
- ➢ The treatment is with 5% permethrin, 1% lindane, benzyl benzoate (application below the neck for upto 3 consecutive days; each application is preceded by a scrubbing bath). Treat all contacts concurrently and wash clothes thoroughly in hot water. Reinfection is frequent.

9

Disorders of the Nervous System

9.1 The central nervous system

OVERVIEW OF ANATOMY OF THE CENTRAL NERVOUS SYSTEM (CNS)

The nervous system has two main parts: the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS roughly corresponds to the portion enclosed within the bony cavities of the skull and vertebral column. More precisely, the PNS begins at the nerve roots arising from the CNS and a small portion of these nerves also lie within the bony confines. The supporting tissue in the CNS is called *glial tissue*: there are *oligodendroglia* responsible for myelination and *astroglia* which work closely with neurons to maintain an optimal environment for neuronal function. In the PNS, glia are not seen and the cells responsible for myelination are called *Schwann* cells.

The CNS has been divided into the brain (the portion rostral to the foramen magnum) and the spinal cord which is caudal to the foramen magnum. The brain is further subdivided based on embryology, structure and function, into the two *cerebral hemispheres,* the central *diencephalon,* the tubular *brainstem,* and the dorsocaudal *cerebellar hemispheres.*

Cerebrum

The cerebrum consists of two halves called the right and left cerebral hemispheres which are separated by an interhemispheric fissure. A dural fold, the *falx cerebri,* lies within the fissure providing support to both halves. If the cerebral hemisphere on one side is disproportionately swollen, it may attempt to pass under the edge of the falx into the opposite compartment thereby exerting pressure on caudal structures such as the diencephalon or brainstem. This is termed a *subfalcine herniation.* The two cerebral hemispheres are connected by a horizontal sheet of nerve fibres called the *corpus callosum.* Despite their anatomical separation, the two cerebral hemispheres work closely together and complement rather than duplicate each other's functions.

A coronal section through a cerebral hemisphere discloses four components: an outermost cerebral cortex (grey matter), a deeper layer of white matter connecting different parts of the cortex, a still deeper layer of masses of grey matter called nuclei (basal ganglia and thalamus) and the innermost ventricular cavities. The cerebral cortex has a large surface area and is therefore folded; the elevations are called *gyri* and the crevices are termed *sulci.* The most prominent sulcus is seen laterally and is called the *sylvian* or lateral fissure. Over the hemispheric surface, parallel to the coronal suture, is the *central sulcus* and on the median surface of the brain, two-thirds of the way from the anterior pole, extending from the upper edge to the corpus callosum is the *parietooccipital sulcus.* These three sulci may be

used to divide the cerebral hemisphere into four lobes (Fig 9.1). The *frontal lobe* lies anterior to the central sulcus and above the sylvian fissure. The *parietal lobe* lies between the central sulcus and the plane of the parietooccipital sulcus and the temporal lobe lies below the sylvian fissure anterior to the plane of the parietooccipital sulcus. The area around the posterior pole and extending upto the parietooccipital sulcus anteriorly is called the *occipital lobe.*

Along the medial surface of the occipital lobe is the *calcarine sulcus,* on either side of which is the primary visual cortex. Anterior to the central sulcus is the *precentral gyrus* which is the primary motor cortex, and posterior to the central sulcus is the *postcentral gyrus* which is the primary somatosensory area. In the depths of the sylvian fissure lies a pocket of cortex called the *insula.* Running transversely across the insula are the transverse temporal gyri (*Heschl's gyri*) which constitute the primary auditory cortex.

A C-shaped ring of cerebral cortex around the corpus callosum constitutes a functionally and embryologically distinct portion called the *limbic lobe* which plays an important role in mood and memory. This is discussed in the section on cognitive neurology. The grey matter nuclei within the cerebral hemispheres have an important role in control of motor movements and are described in the section on movement disorders. A brief overview of diencephalic structures is given below.

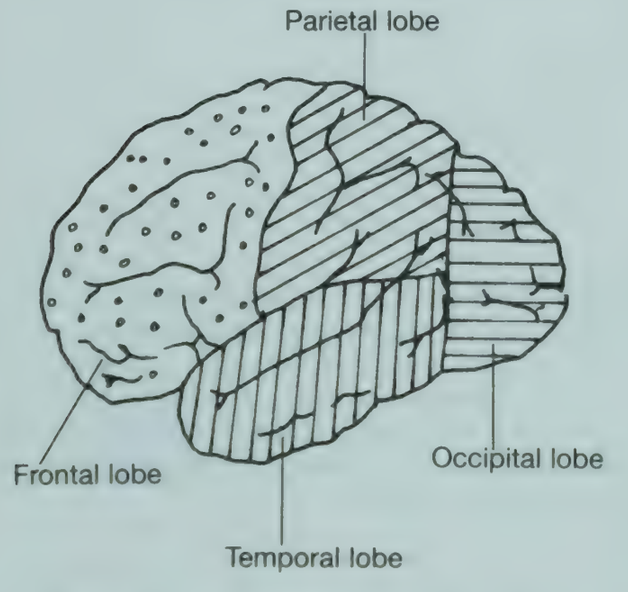

Fig 9.1 The lobes of the cerebral cortex

Diencephalon

In the process of embryological development, the roof of the third ventricle develops into the *epithalamus* which has little representation in the adult (pineal body and adjacent commissures). The sides of the third ventricle are formed by two egg-shaped and egg-sized masses, each called the *thalamus,* which function as the relay zone for fibres passing to and from the cerebral cortex. The thalamic nuclei are divided into groups. The ventral thalamic nuclei relay afferent somatosensory (ventroposterolateral and ventroposteromedial nuclei) and somatomotor (ventral anterior and ventrolateral nuclei) pathways. The dorsal and medial thalamic nuclei project diffusely to different parts of the cerebral cortex and receive input from the ascending reticular activating system. Their role appears to be in regulating consciousness, the sleep–wake cycle and alerting responses. The posteriormost part of the thalamus is called the *pulvinar* and attached to it are two rounded structures called the medial and lateral *geniculate bodies.* These serve as relay stations for the auditory and visual pathways respectively.

The floor of the third ventricle is made up of the *hypothalamus.* The hypothalamus extends from just anterior to the optic chiasma to the mammillary bodies posteriorly. It is divided into a number of nuclei all of which serve to control vegetative and autonomic functions such as appetite, fluid intake, regulation of body temperature, sleep–wake cycle and sympathetic and parasympathetic functions. The hypothalamus also regulates the function of the pituitary thereby serving as a bridge between the nervous and the endocrine systems.

Lateral to the hypothalamus and inferior to the thalamus is a small area called the *subthalamus* which carries fibres passing to and from the basal ganglia to the midbrain. This area appears to be functionally integrated with the basal ganglia and will be discussed in the section on movement disorders.

Brainstem and Ventricular System

The brainstem is divided into three areas. Rostrocaudally, these are the midbrain, the pons and the medulla oblongata. The ventricular system consists of paired *lateral ventricles* (one in each cerebral hemisphere) both of which open through a narrow foramen (*foramen of Munro*) into a central slit-like *third ventricle* within the diencephalon. A narrow tubular aqueduct (aqueduct of Sylvius) runs through the midbrain and expands in the pontomedullary region to form the *fourth ventricle.*

Dorsal to the fourth ventricles lie the cerebellar hemipheres. Superiorly, the cerebellar hemispheres are separated from the occipital lobes by a dural fold, the *tentorium cerebelli.* The anterior surface of the tentorium has a notch to accommodate the midbrain as it passes caudally. The anteromedial portion of the temporal lobe, the *uncus* or temporal pole, overhangs the lateral edges of the tentorium. An increase in intracranial pressure rostral to the tentorium can push the uncus downwards resulting in compression of brainstem structures (*uncal herniation*) (Fig 9.2). The caudalmost portions of the cerebellum are called the *tonsils.* An increase in pressure in the infratentorial compartment can push the tonsils through the foramen magnum compressing adjacent parts of the medulla and spinal cord (*tonsillar herniation*). The structure and function of the cerebellum is discussed in the section on disorders of the cerebellum.

BLOOD SUPPLY TO THE BRAIN

Arterial supply to the brain

The brain receives its blood supply from four pairs of arteries— two vertebral arteries and two internal carotid arteries. These four arteries penetrate foramina in the base of the skull to approach the brain ventrally (Figs 9.3, 9.4). The two vertebrals supply the medulla and cerebellum and fuse at the caudal end of the pons to form a large midline basilar artery which supplies the upper cerebellum and pons. Branches arising from the top of the basilar artery supply the midbrain, thalamus and posterior portions of the basal ganglia and internal capsule. Finally the basilar artery

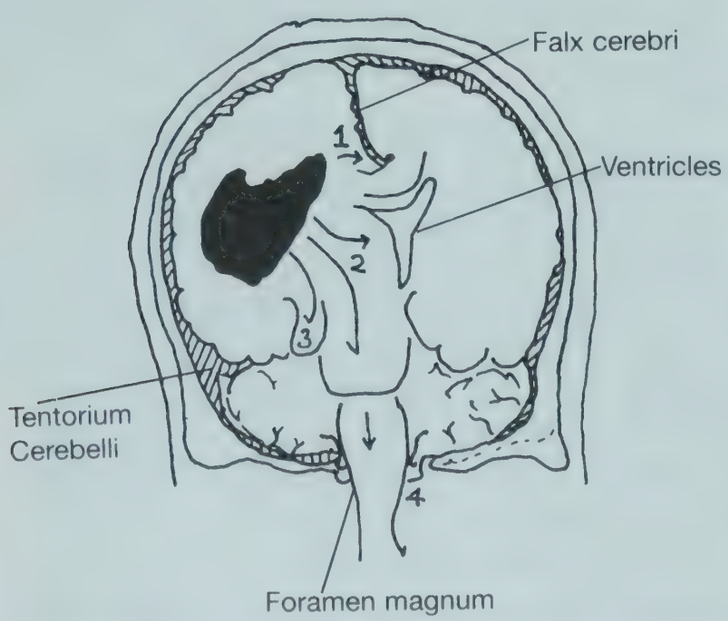

Fig 9.2 Brain herniations secondary to mass lesions: 1. subfalcal herniation where the cingulate gyrus shifts under the falx cerebri; 2. central herniation with downward displacement of the diencephalon; 3. uncal herniation in which the medial temporal lobe is displaced through the tentorial opening; and 4. herniation of the cerebellar tonsils through the foramen magnum

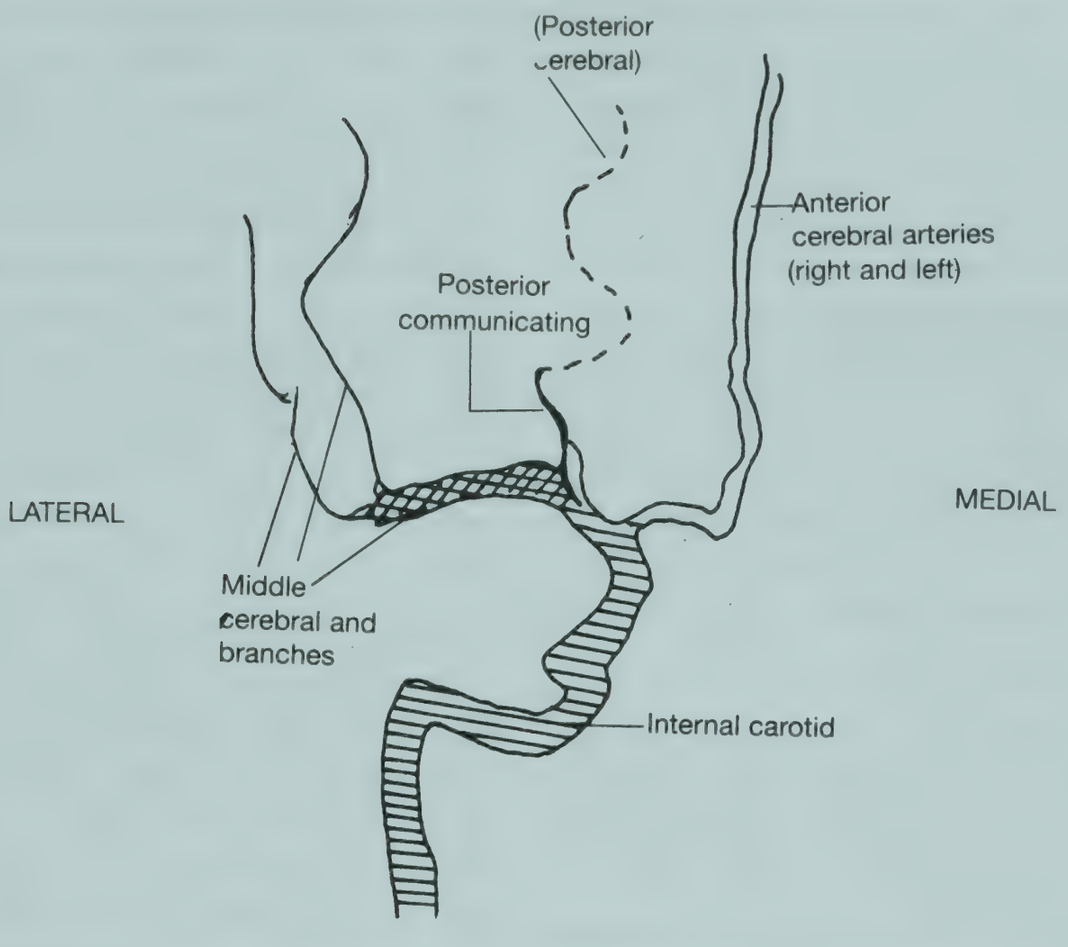

Fig 9.3 Anteroposterior view of a carotid angiogram (looking through the forehead)

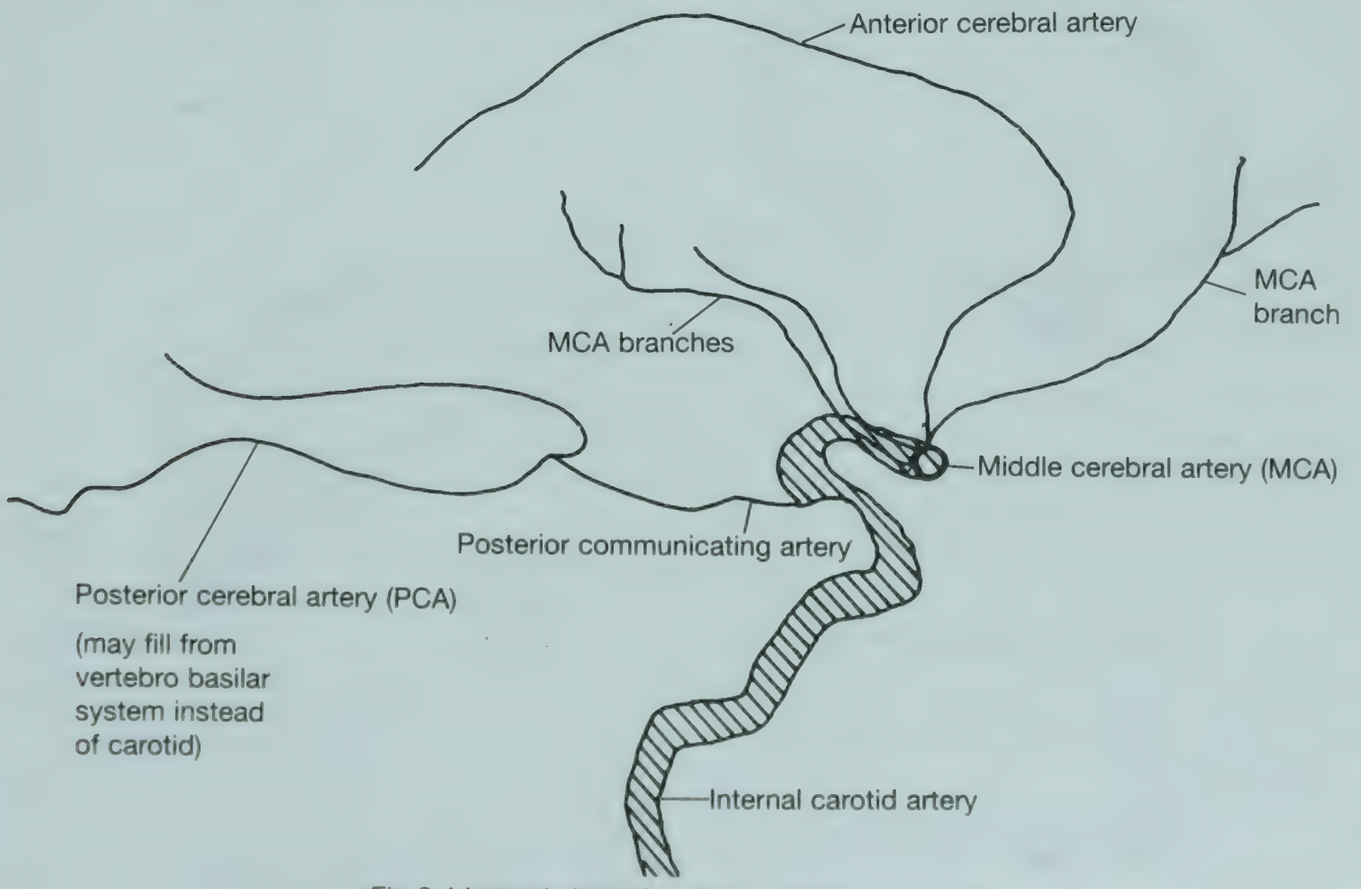

Fig 9.4 Lateral view of a right carotid angiogram

bifurcates into two posterior cerebral arteries which supply the occipital lobes. En route, the posterior cerebral arteries give off the posterior communicating arteries which join the carotids to form the *anastomotic circle of Willis*. The internal carotids supply ophthalmic branches to the eye and divide superiorly into a large middle cerebral artery and a small anterior communicating artery. The middle cerebral artery supplies most of the lateral surface of the cerebral hemisphere. The anterior communicating arteries fuse and give rise to one or two anterior cerebral arteries which supply the medial and inferior frontal surfaces. Perforating branches from the anterior and posterior communicating arteries supply the diencephalon. Penetrating vessels from the proximal middle cerebral artery supply most of the putaminocaudate region and internal capsule. Fig 9.5 shows the blood supply, both the arterial and venous systems, to and from the different areas of the brain.

Venous drainage of the brain

The veins of the brain, unlike those of other organs, run independent of the arteries and freely anastomose. There are four venous systems: the superficial veins, the penetrating or intraparenchymal veins, the deep veins and the intradural sinuses. The intradural venous sinuses ultimately receive all the venous blood and empty into extracranial veins through *emissary veins*. The emissary veins pass through foramina in the skull. The most important of these is the jugular vein which is a continuation of the *sigmoid sinus* and passes through the jugular foramen. The intradural sinuses are the superior and inferior sagittal sinuses within the falx cerebri, the lateral sinuses at the attachment of the tentorium to the bone and the sigmoid sinus which passes inferiorly from the transverse sinus to the jugular vein lying close to the mastoid. The veins from the inferior surface of the cerebral hemispheres drain into a cavernous sinus lying in the parasellar region.

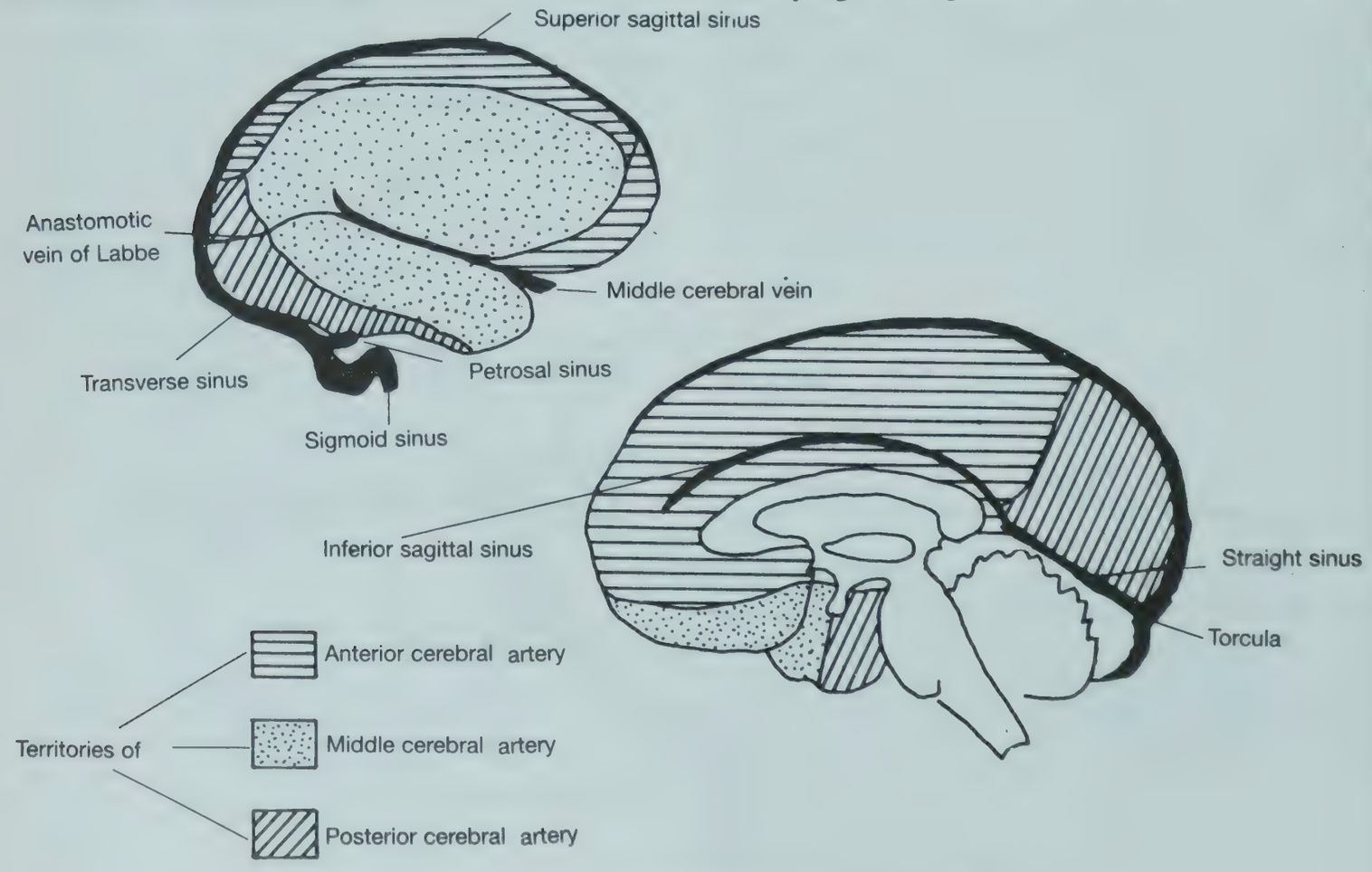

Fig 9.5 Arterial blood supply and venous drainage

Cerebral metabolism and blood flow

The brain uses a large amount of energy for its various activities such as driving the Na-K ATPase and other energy-dependent membrane ion pumps, and the synthesis and release of neurotransmitters. Unlike the muscles, the brain has no glycogen energy stores and is critically dependent on a sizeable blood flow. Blood flow to the brain is 60 ml/100 g of brain tissue per minute or 20 per cent of the stroke volume. Hypercapnia causes dilatation of cerebral arterioles, increasing flow rates.

The brain can only use circulating glucose (or in rare instances, ketone bodies) as its energy source. The resting brain extracts 10 per cent of the available blood glucose (glucose extraction ratio) and 50 per cent of the available blood oxygen (oxygen extraction ratio). Increased synaptic activity is associated with a simultaneous increase in blood supply to the area.

Blood-brain barrier

The normal function of the brain requires that the ionic and molecular composition of the extracellular spaces within the brain be strictly regulated. This is the function of the blood-brain barrier. The constituents of this barrier are shown in Fig 9.6. The critical structure is the specialised endothelium which lacks transendothelial channels so that all substances have to pass through the cytoplasm of the cell. Other constituents include the basal membrane and the astrocytic foot processes. Lipid soluble substances and gases can diffuse freely across this barrier and glucose is transported using a special carrier. Most other substances are kept out.

If there is a break in the blood-brain barrier, there is entry of plasma proteins and cells into the brain, and this may be reflected in the CSF on lumbar puncture. The entry of osmoles into the brain may also cause brain edema (vasogenic edema). If the barrier is intact, polar molecules cannot enter the brain; hence agents such as dopamine have to be administered in a precursor form (l-dopa) which can enter the brain. Other substances may have to be administered intrathecally (for example, methotrexate, in the treatment of acute lymphocytic leukemia). On the other hand by choosing a drug that would not enter the brain we can prevent central side effects from a systemically administered drug (for instance, neostigmine used for the treatment of myasthenia gravis, does not enter the brain).

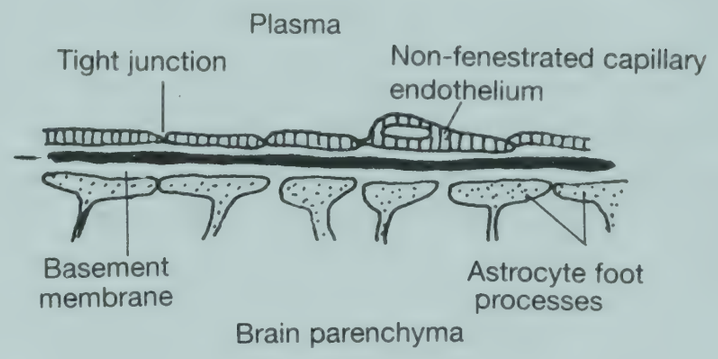

Fig 9.6 The blood-brain barrier

SYNAPTIC NEUROCHEMISTRY

The synapses are the primary facilitators of interneuronal information transfer. Most synapses are chemical. Each consists of a specific region where the membranes of two neurons are in close approximation. A chemical messenger released from one membrane (the *presynaptic membrane*) diffuses across the intervening space (*synaptic cleft*) to act on a specific receptor on the opposing membrane (the *postsynaptic membrane*). The chemical messenger may act on 'autoreceptors' on the presynaptic membrane as well. These chemicals are called *neuroregulators* and may be functionally divided into two types, neurotransmitters and neuromodulators. *Neurotransmitters* are released and bound only at the synapses and act rapidly.

Neuromodulators may be released from synaptic or non-synaptic membrane locations and may diffuse locally to affect several adjacent neurons. Their effects are slower but last longer and include modification of neuronal response to neurotransmitters.

Neurotransmitters may be solely excitatory (glutamate, aspartate) or solely inhibitory (gamma amino butyric acid–GABA, glycine). Others may function either way depending on the location of the synapse, the receptor subtype involved and the state of the neuron which is being affected.

The major neuroregulators, their metabolism and receptor subtypes, agonist and antagonist agents are summarised in Table 9.1. Other neuroregulators include GABA, glycine, glutamate, aspartate, histamine, adenosine and various peptides (opiates, CCK, somatostatin, thyrotropin-releasing hormone, substance P, vasopressin and VIP-vasoactive intestinal peptide).

Table 9.1 Neuroregulator

Chemical	*Major pathway*	*Receptors*	*Metabolic enzymes*	*Comment*
Biogenic amine: Dopamine	Nigrostriatal	2 subtypes	MAO (monoamine oxidase type A and B)	Dopamine deficiency causes 'Parkinsonian features'; excess causes hallucinations/ psychosis. Neuroleptic agents deplete dopamine.
Biogenic amine: Noradrenaline (NA)	Most brain noradrenergic projections arise from the 'locus ceruleus' in the pontine tegmentum; also in sympathetic nervous system	2 major classes– α and β, each with 2 subtypes	MAO-A	Depletion causes depression; NA mediates sympathetic tone–hence MAO-A inhibitors cause hypertensive crisis; selective MAO-B inhibitors (Selegeline) do not.
Acetylcholine	From the nucleus basalis via the medial forebrain bundle to the cortex; the autonomic nervous system	2 major classes– muscarinic and nicotinic; over 5 subtypes	Cholinesterase	Different types of cholinesterase inhibitors may be therapeutic (Myasthenia, Alzheimer's) or toxic (organophosphorus)
Biogenic amine: Serotonin	Most serotoninergic projections arise from the dorsal raphe nucleus in the pons	4 receptor subtypes	MAO-A	Sumatriptan, cyproheptadine and methysergide, all drugs used to treat migraine, are serotonin antagonists

9.2 Approach to a patient with neurologic disease

The signs and symptoms of nervous system dysfunction are frequent, varied and complex. There are a large variety of neurologic disorders. Fortunately, only a few are common and a few others are important, though rare.

The key to evaluating patients with neurological symptoms is their history. It has been stated that 95 per cent of the diagnosis depends on the history. However, taking a neurological history requires perhaps more skills than in examining any other organ system. This is because the very pathology which results in symptoms may also affect the patient's ability to give a history. Thus, a patient who is confused, comatose, has an impaired memory, has a speech difficulty, or is depressed cannot give a reliable history. With patience and perseverance, interviewing family, friends and bystanders, contacting previous physicians and reviewing all available records, a remarkable amount of detail may be gathered.

During the process of taking a history and, later, of examining the patient, hypotheses are constantly generated and tested by asking further questions. Hypothesis generation should begin by identifying a complete list of presenting symptoms and deciding which particular neurological system is most likely to generate these symptoms (for instance, *Is this a cognitive problem, a movement disorder or a neuromuscular problem?*). The second step is to decide on an anatomical localisation (*Where is the lesion*: for example, the dominant cerebral cortex, the posterior fossa or the median nerve). In determining the anatomical localisation, the *distribution* of symptoms and signs is most helpful. The third step is to consider the various pathological processes which can occur at this anatomical localisation (what is the likely pathology). In this determination, the *time course* of symptoms is very helpful; for instance, a stroke would become manifest over hours and a degenerative dementia over months. The fourth step is to attempt to explain all the symptoms and signs in terms of the given pathology using what is known about the pathogenesis of these symptoms and signs (for example, is the sudden deterioration of sensorium in the patient with a small brain tumour due to a hemorrhage into the tumour). It is also important to assess the functional deficits and residual function. Finally, it is useful to assess any risk factors (reversible or irreversible) which may be contributing to the pathology. While eliciting a history, it is also important to take a family history, a drug history and a history of past and associated medical illnesses since the nervous system is closely integrated with other organ systems. While gathering the history the examiner can also form a general impression of the patient's personality, intelligence, and motivation. The examiner should clarify with the patient and family their perceptions regarding the illness and their expectations from the encounter.

A truly complete neurological examination is a formidable task for the examiner as well as for the patient. Instead, the history may be used to

orient the examination so that a complete examination of all relevant portions of the nervous system is made. In addition, the rest of the nervous system is screened for problems and a more detailed evaluation performed when indicated. There are numerous tests which will be outlined under each section and can also be gathered from textbooks on examination, peers, teachers and above all, the patient. A screening neurologic examination is usually sufficient for the 'healthy' patient such as someone coming for a routine physical examination. Such an examination is brief, takes approximately ten minutes and involves cognitive assessment during history-taking, evaluation of pupillary response, eye movements while following the examiner's fingers, examination of the fundi, facial sensation and movement, speech, strength in the upper limbs (hand grip and shoulder abduction) and lower limbs, tendon and plantar reflexes, pain and vibratory sensation in the feet and gait.

While recording the examination it is useful to describe what was done and what was observed rather than to apply a poorly-defined medical term. Thus, it is better to say that the patient woke up when he was pinched than to say that the patient was stuporose.

Once a diagnostic hypothesis has been made and a list of differential diagnoses arrived at, laboratory tests are selected which will help confirm the chosen diagnosis and/or exclude potentially serious differential diagnoses with a minimum investment of time, patient risk and discomfort, and money.

In this section we discuss some common neurologic problems which provide a practical illustration of how the above principles are applied.

APPROACH TO A PATIENT WITH HEADACHE

Headache has been described as the most common medical complaint among humans. Nearly all adults have experienced a headache at sometime or other, in their lives. Nearly 5 per cent of the population suffers from recurrent headaches. Most individuals do not even consult a doctor but treat their own headaches with rest, food, exercise, coffee or an analgesic. However, a headache can also be the first symptom of a life-threatening illness such as meningitis, subarachnoid hemorrhage or a brain tumour. Thus the challenge in evaluating these patients is in separating the grain from the chaff—the relatively small number of patients with a life-threatening illness from the vast majority with a less serious cause. In the latter, management consists of reassuring the patients and optimising the quality of their life with the judicious use of appropriate medication.

Pathophysiology A headache may be defined as a pain perceived over the region of the cranial vault. It is a fascinating fact that the brain parenchyma, much of the meninges and the bony skull have no capacity to feel pain. Where then does a headache arise? Pain-sensitive structures in the head include the arteries within the meninges, the dura at the base of the brain, the dural sinuses, the periosteum of the skull, the muscles of the scalp, the eyes, teeth, paranasal sinuses and skin. Pain stimuli from the face and from intracranial structures above the tentorium are carried by branches of the trigeminal nerve. The innervation of structures in the posterior fossa is by the ninth and tenth cranial nerves and the first three cervical nerves. Headache can occur whenever there is dilation of intracranial arteries[1] (as in hypertension), traction or compression of pain-sensitive structures (as in a brain tumour), inflammation of the meninges (as in meningitis) or spasm of the cranial or cervical musculature (as in tension headaches).

1 Most pain-sensing nerve endings of the trigeminal nerve lie in the wall of the meningeal vessels.

Causes of headaches are listed below:

1. Migraine
2. Tension headache
3. Cluster headache
4. Space occupying lesions (tumour, tuberculoma, brain abscess etc.)
5. Temporal arteritis
6. Meningitis
7. Stroke: Subarachnoid hemorrhage, intracranial hemorrhage, large infarct
8. Head trauma (concussion, contusion, subdural hematoma, extradural hematoma)
9. Trigeminal neuralgia, postherpetic neuralgia
10. Medical illness (hypertension if diastolic > 110 mm Hg; fever etc.)
11. Postlumbar puncture headache
12. Medication (nitrate, hydralazine), alcohol
13. Miscellaneous (referred from sinuses, teeth, eyes, ears, ears, cervical spine)

History: Headache is a subjective complaint. A good history is essential for making the correct diagnosis. The patient is asked if this is the first severe headache or if this headache seems atypical for that person. If so, a serious etiology is more likely. If not, the patient should be asked to describe a single typical headache, the types of headaches suffered, and to draw up a temporal profile of the headaches (when they occur and how long they last). The description of the headaches should include how it began, where it is felt, how severe it is and what associated symptoms occur. If the patient suffers from more than one type of headache a separate description should be obtained of each type. A history of alcohol or drug (including prescription medication) intake should be explored.

Onset: An extremely sudden onset of a severe headache (apoplectic onset) strongly suggests intracranial hemorrhage. Awakening with a headache, particularly if it occurs very often, should prompt a consideration of a brain tumour, a sleep disorder or a sinus headache. Most headaches begin insidiously towards midday. Awakening in the middle of the night with a severe headache for several nights in a row, suggests a cluster headache.

Location: One should enquire if the headache is unilateral or bilateral, occipital, frontal or temporal. The commonest type of headache is bilateral over the frontal or vertex areas. A unilateral temporal headache is more common with migraine (but may also be seen with other headaches). Such a headache in an elderly person should suggest temporal arterits. The headache of a subarachnoid hemorrhage is often occipital and associated with neck stiffness. However, most occipital headaches are benign being due to migraine or tension. With trauma or a tumour, the headache may roughly overlie the lesion or be bilateral.

Severity: The severity of a headache as described by a patient is as much an index of his or her personality and attitude towards the pain as of the severity itself. The patient is asked to describe the intensity of the pain on a scale of one to ten, where 1 is the mildest and 10 the most severe pain felt. This assessment is helpful in comparing response to therapy. The true severity of a headache is often best assessed by enquiring regarding its effect on the lifestyle of the patient — does it interfere with sleep, work, school, household responsibilities? A headache which interferes with the patient's lifestyle is likely to be more severe than one which does not.

Duration: Brief fleeting pains and headaches which have lasted for several years in an 'on and off' fashion are less likely to represent a serious pathology.

Associated symptoms: If a patient has dizziness or syncope with a sudden-onset headache, a subarachnoid hemorrhage should be suspected. Presence of ipsilateral ptosis suggests an aneurysm of the posterior communicating artery. Presence of fever and altered sensorium raises the concern of an intracranial infection. On the other hand almost any febrile illness can cause a

headache; a benign headache would be less severe, would not cause altered sensorium and would respond to lowering of the temperature. Mild cognitive dysfunction, nausea, vomiting and episodes of blurred vision suggest headache due to raised intracranial tension, especially if the headaches are of recent onset and occur frequently. Migraine with aura causes more dramatic visual symptoms such as coloured lights and lines. Pain associated with unilateral 'tearing' suggests a cluster headache.

Periodicity and precipitating factors: Daily headaches of recent onset are more likely to be serious while chronic daily headaches are almost always tension headaches. A single episode of unremitting pain over more than a day suggests a hemorrhage, meningitis or temporal arteritis. In a brain tumour the headaches gradually increase in frequency and severity over time. Migraine typically has a frequency of one attack every few months to 2–3 per month. In a woman, an attack may occur every month close to the menstrual period. Migraine may also be precipitated by a variety of foods. Cluster headaches may occur almost every night for several weeks. Pain brought on by stooping may arise in the sinuses; that brought on after a movie (dim light) or eye-strain may be due to glaucoma or an uncorrected refractory error. Pain precipitated by poor posture at work is usually a tension headache. Pain related to chewing may be seen with dental problems or temporal arteritis. All types of headaches are more likely when the patient is hungry, tired or stressed. A variety of medications can cause headache; a common example is isosorbide dinitrate given to treat angina. Alcohol withdrawal can cause a headache ('hangover').

Examination A complete neurological examination is warranted in any patient presenting with recent onset headaches or a change in headache pattern. The general examination should include a record of the body temperature, blood pressure, peripheral pulses, looking for tenderness or nodularity over the temporal arteries, evaluation of the skull, scalp and face for signs of trauma, examination of the sinuses for tenderness on pressure, examination of the teeth and a brief evaluation to rule out cardiac, respiratory or renal failure all of which can cause headache. The neurological examination should always include evaluation of visual acuity, fundus examination for papilledema and hypertensive changes, examination of the ear drum and hearing, looking for neck stiffness, assessment of the cervical spine, tendon reflexes, plantars, gait and tandem walk.

Investigations The number of investigations ordered and the speed with which they are pursued depends on the clinical assessment. The evaluation of a patient with suspected meningitis or subarachnoid hemorrhage is dealt with in the respective sections. In many patients with chronic headache and a reliably normal neurological examination (that is, when the neurological examination has been meticulously conducted and found normal) no investigations may be required if the history is typical for migraine or tension headaches. Screening investigations may include a blood count and ESR; rarely, a CT scan, sinus X-rays or evaluation by an ophthalmologist (for glaucoma, refractory error, convergence insufficiency) may be sought.

Migraine

Migraine may be described as a disorder characterised by episodic headaches of a typical clinical pattern with or without associated visual and gastrointestinal symptoms.

Clinical features There are two main types of migraine. The first, migraine without aura (previously called common migraine), is characterised by headache of 4–72 hours duration which is usually severe (grade between 7–10) but may be moderate, usually unilateral

but sometimes bilateral and typically accompanied by nausea (with or without vomiting), photophobia (hypersensitivity to light) and phonophobia (hypersensitivity to sound). The headache may have a pulsating quality and is often exacerbated by physical activity so that the patient may prefer to stop working and to lie down in a quiet, dark room.

The second type is migraine with *aura* (previously called classical migraine). The headaches are heralded by neurological symptoms called aura. An aura is most typically a positive visual phenomenon and descriptions include bright lights and wavy lines. Images of their aura drawn by artistically inclined migraine sufferers sometimes have a striking resemblance to psychedelic abstract art. Such positive visual phenomena may be accompanied by visual field defects and such aura are described as 'scintillating scotomata'.[1] Aura may also be experienced in terms of sensory, speech or motor symptoms. The headache follows the aura and is similar to that described for migrane without aura.

Migraine typically affects patients for a major part of their lives. Typically the onset of attacks begins before the age of 20. In children the nausea and vomiting is often prominent and the attacks may be diagnosed as 'gastroenteritis' or 'indigestion'. Such attacks are sometimes called 'abdominal migraine'. The frequency of attacks may vary greatly from a maximum of 2–3 attacks per week to an attack free period which may last for several years. Typically sufferers have 2–20 attacks per year.

Aggravating and relieving factors: A variety of factors can precipitate an attack of migraine in any patient with a propensity for migrainous attacks. By maintaining a diary, a patient can usually identify these factors. A perimenstrual occurrence of the headache is common in women (*catamenial migraine*). Certain foods (chocolate, cheese, red wine, fatty substances, canned foods) can precipitate the headache. Hypoglycemia, sleep deprivation, air travel and caffeine withdrawal can cause headaches as can stress. The use of oral contraceptives is a common precipitating factor. Pregnancy may transiently relieve the attacks. There is often a perimenopausal exacerbation of headaches with almost complete resolution after menopause.

Variants of migraine: In a few patients, an attack of migraine may be followed by a transient neurologic deficit, commonly a hemiparesis lasting for 1–2 days. Such an attack is called a *complicated migraine*. If dysarthria and vertigo are part of the aura, a diagnosis of basilar migraine is made. Patients with ophthalmoplegic migraine have ptosis or abducens nerve palsy with each headache. Before diagnosing any of these variant syndromes, more common etiologies such as stroke or subarachnoid hemorrhage must be ruled out.

Epidemiology Approximately 15 per cent of the population has experienced a migraine headache at sometime in their lives; approximately 10 per cent of young adults have had a migraine in the past year. Only a third of these are with an aura (classical).

Pathophysiology Migraine is classically associated with occipital hypoperfusion which begins simultaneously with the onset of the aura. This hypoperfusion gradually spreads forward to contiguous areas without respecting arterial boundaries. It has been found that the regional hypoperfusion is secondary to the depolarisation of cortical neurons and glial cells in the same area. This wave of 'depression' (the depolarised neurons are less readily activated) which spreads over the cortical surface has been called *Leao cortical spreading depression*. What precipitates this neuronal depolarisation is not clear. The hypoperfusion lasts throughout the aura and well into the headache phase; thereafter, there

[1] Other names for the light patterns include *fortification spectra* or *teichopsia*.

hyperperfusion during which the headache resolves. The hypoperfusion, the aura and the headache all usually occur on the same side. This 'cortical spreading depression' is not seen in migraine without aura.

Paradoxically, the cortical hypoperfusion is associated with dilatation of larger intracranial and extracranial vessels. The pain in migraine, is thought to arise from trigeminal nerve endings in the walls of the dilated arteries. Stimulation of the trigeminal (Gasserian) ganglion can in turn lead to release of sensory neuropeptides—serotonin and substance P— within the arterial wall. These peptides cause a 'neurogenic inflammation'. Migraine is associated with an initial rise in plasma serotonin (probably arising from platelet breakdown) followed by a decrease in serotonin levels. How all these different pieces of the migraine puzzle fit together is not yet clear.

A very small subgroup of migraine called familial hemiplegic migraine has been associated with a locus on chromosome 19. Although a family history can be elicited from approximately 50 per cent of migraine sufferers, the role of genetics and of psychic factors in the pathogenesis of migraine is not yet clear.

Management The first step is confirmation of the diagnosis. If the patient is below 30, has had typical attacks of 'migraine with aura' for over an year and has no abnormal findings on a meticulously thorough neurological examination, no further investigations are usually neccesary to establish a diagnosis of migraine. If the patient has had an imaging study at some time in the past, subsequent to the onset of at the headaches, and the study was normal, it is not necessary to repeat the study unless there is a dramatic change in the pattern of the headaches or a new finding on the neurological examination. Migraine without aura and tension headaches may be very similar and may occur in the same individual.

The goals of migraine treatment are amelioration of the symptoms of an acute attack and prevention of further attacks, either by behavioural or pharmacological means. The behavioural approach includes advising regular habits of sleep, mealtimes and light aerobic exercise, and avoidance of initiating factors such as drugs, alcohol and excessive caffeine. Family or work-related stress and emotional problems should be explored. If these are unavoidable, stress management and relaxation techniques can be taught. The patient should be encouraged to maintain a headache diary (like the one shown in Fig 9.7) since this is very useful in identifying correctable factors and in assessing the response to prophylactic medication.

Drug therapy (Table 9.2) In case the need for symptomatic treatment for an acute attack arises, the mildest, least toxic, least addictive analgesic agent which is effective in the given patient should be used. The patient's cooperation should be sought during the period

Date	*Time of onset of headache*	*Precipitating factors (if any) (diet, stress, medication, menstruation)*	*Severity (1–4) (1: mild, 2: moderate, 3: severe, 4: excruciating)*	*Treatment taken (non-drug sleep/ exercise)*	*Time of cessation of headache*

Fig 9.7 A headache diary

when this agent is being determined. The same drug can then be used for management of all subsequent acute attacks for several years.

Aspirin, acetaminophen, NSAIDs and mild narcotics such as propoxyphene and codeine are all sometimes effective in the management of migraine. The most commonly used NSAIDs are ibuprofen, naproxen and mefenamic acid. They have the potential for causing dyspepsia and rarely, gastrointestinal hemorrhage. Narcotics (such as Proxyvon which contains dextroproxyphene) are often initially effective but frequent use can lead to a pattern of less severe but more frequent headaches. This is because these agents have addictive potential and a propensity to induce withdrawal headaches.

Because gastric stasis often accompanies migraine attacks, metoclopramide, a drug that promotes gastric emptying, enhances the effectiveness of analgesic medication and reduces nausea. Other antiemetic agents which may be given along with the analgesic medication include perphenazine and prochlorperazine. All these agents can in rare cases cause dystonia, particularly in children and adolescents.

In severe migraines none of the above may be effective. The two most effective and specific agents are ergot and sumatriptan. Ergotamine is available as a 1 mg tablet in combination with caffeine (Cafergot, Vasograin) and as a suppository. Caffeine increases absorption and, perhaps, the efficacy of ergot. The usual oral dose is 2 tablets at the first signs of a headache to be followed by one additional pill after half an hour and a further pill after an additional hour if the headache persists. The maximum weekly dose should be less than 10 mg. Ergotamine is a serotonin agonist and also a vasoconstrictor. Hence, it is contraindicated in patients with coronary artery disease and peripheral vascular disease and in pregnancy. Another distressing side effect is precipitation of nausea, vomiting and abdominal pain. To avoid this, the oral pill may be given with metoclopramide or the suppository may be used. Oral ergot is effective in 50 per cent of patients.

Sumatriptan is a serotonin receptor agonist which is most specific for the 5-HT_{1D} receptor. It is administered subcutaneously as a 6 mg dose at the onset of the attack. The drug is available as preloaded, self-administrable injections. Sumatriptan relieves the headache in 75 per cent of patients but half of them will experience a recurrence of the headache in 24–48 hours, neccessitating administration of a second dose. The first dose is given in an emergency room or a doctor's office as many patients experience distressing symptoms of flushing, warmth, heaviness in the chest and pain. These symptoms are usually transient and benign but may recur with each injection. Fatal myocardial infarction is a very rare complication which has been described. Hence, sumatriptan is also contraindicated in patients with coronary artery disease. Recently oral sumatriptan has become available. The effective dose is 25 mg to 100 mg per attack. Oral sumatriptan is expensive but not prohibitively so.

Prophylactic therapy: The principles of prophylactic therapy are:

1. The patient should have frequent disabling headaches (usually more than 2 to 3 each month) and feel a need for prophylactic medication.
2. The physician should first correct as many reversible factors as possible, for example, vasodilators such as isosorbide dinitrate and hormones such as birth control pills which may precipitate headaches.
3. Each physician should consistently use some prophylactic medication (amongst the many choices) which he is familiar with in terms of doses, side effects and possible drug interactions. The choice in an individual patient depends on the medical history; a patient with asthma should not receive a beta-blocker, a patient with mild hypertension would benefit from a beta-blocker or calcium-channel blocker. The most

frequently used first-line agent is propranolol.

4. Cost is an important consideration since prolonged treatment may be required.
5. The chosen medication needs to be given for a sufficient period of time to judge its effectiveness. This period is usually 2 to 3 months. Starting at the lowest dose, the maximal dose is reached in 2 or 3 increments. Doses are typically increased after a month's trial of the lower dose.

Common Headaches or Tension-type Headaches

The commonest type of headache is suprisingly the least well-defined with regard to its pathology. Headaches which do not fit into any of the previously defined groups are called 'tension-type headaches'. Often, but not invariably, one may identify emotional or physical stress which precipitates the headache. Muscle contraction may be palpable in the temporalis and cervical paraspinal musculature. Less commonly, the trapezius ridge is tender. Pressure or massage over these areas may relieve the pain. Most headaches are mild to moderately severe, bilateral and may be described as a 'band-like' pressure over the head. They typically begin towards evening and last for several hours, respond at least partially to any common analgesic and disappear after a good sleep. Management consists of a well-tolerated analgesic agent (aspirin, paracetamol, ibuprofen) at the lowest effective dose. If the headaches are frequent, antidepressant medication such as amitriptyline and imipramine

Table 9.2 Drugs used to prevent migraine

Type of drug	*Dose*	*Side effects*
Beta-adrenergic blocker: Propranolol (regular or long acting), atenolol, metoprolol	40 to 160 mg per day of propranolol	Fatigue, depression, hypotension, bronchospasm. In diabetics, a theoretical possibility is that Propranolol could mask the symptoms of hypoglycemia, such as tachycardia and sweating, leading to dangerously low glucose levels
Calcium-channel blocker: Nifedipine, Verapamil,	10 to 30 mg of Nifedipine per day;	Nifedipine: Tachycardia, pedal edema, hypotension
Diltiazem, Nimodipine	40 to 240 mg of verapamil per day	Verapamil: bradycardia, constipation
5 HT influencing: Methysergide	2 to 8 mg/day	Can cause retroperitoneal, cardiac valvular and pleural fibrosis, hence rarely used. 3 month periods on drug must be followed by 1 month break. Avoid prolonged use.
Amitryptyline	10 to 150 mg/day	Dry mouth, drowsiness, cardiac arrhythmias, urinary retention
NSAID: Naproxen, Mefenamic acid	rarely used	GI bleeding
Miscellaneous: Valproate	400 to 1000 mg/day	Alopecia, hepatic dysfunction, teratogenicity
Prednisone, Clonidine, Phenytoin, Cyproheptadine	based on anecdotal evidence	

5HT = 5-hydroxytryptamine
For menstrual migraine, prophylactic therapy may be limited to the perimenstrual period. Oral contraceptives may help this group. Diuretics have been tried in the premenstrual period but do not help much.

may be useful in reducing the frequency of the attack. These drugs are discussed in the chapter on psychiatry. A clinical diagnosis of depression is not necessary for this medication to be effective. It is possible that the effect of the drug on monoaminergic neurotransmission directly benefits the headaches. The medication should be started at a low dose and very gradually increased, otherwise the patient will have side effects of sedation and dry mouth and will stop complying with treatment. There is no clear line separating migraine and tension headaches. Often the most recalcitrant tension headaches are in patients who begin with a pattern suggestive of migraine and then over a period of time develop daily headaches. In these patients, the cause of the daily headaches is their dependence on analgesics. Any analgesic (opiate, ibuprofen, aspirin) can, when used several times each day, lead to withdrawal headaches for which the patient then needs to take more analgesics. While explaining this to the patient with empathy, one can often persuade the patient to spend a week off all medication after he has been started on prophylactic medication against migraine. The patient may be admitted or support provided at home. There are severe headaches in the early part of the week but thereafter the frequency may drastically diminish. If the initial headaches were responsive to specific migraine medication (ergotamine, sumatriptan), then that medication may be used judiciously to control the pain during the week of withdrawal.

Cluster Headaches

These are also called paroxysmal nocturnal cephalalgia or Horton's syndrome. The typical patient is a young man. The characteristic headaches are severe, unilateral, beginning behind the eyeball and spreading to involve the frontotemporal region. There is associated redness, pupillary constriction, ptosis and tearing in the ipsilateral eye and ipsilateral nasal stuffiness. The headaches tend to occur every night, 2 to 3 hours after the patient goes to sleep, for several weeks (hence the name 'cluster') followed by a headache-free interval of months to years. The mechanism is thought to be vascular, perhaps related to the abnormal release of histamine. Interestingly, these headaches seem to occur only during REM sleep.

Temporal Arteritis

This diagnosis should be considered in every elderly patient who presents with unexplained headaches. Migraine beginning at this age is unusual. Temporal or giant cell arteritis is due to inflammation in one or more branches of the carotid artery. It has an incidence of 1 in 5000. Any type of headache can occur but scalp tenderness or tenderness over the temporal artery suggests the diagnosis. There may be associated transient visual obscuration, proximal muscle weakness and muscle aches (called polymyalgia rheumatica) or fever. The greatest danger is occlusion of the retinal artery resulting in blindness. The diagnosis can be made by the markedly elevated ESR which is often over 100 mm/hr (a value less than 40 mm/hr is rare in untreated temporal arteritis) The diagnosis may be confirmed by biopsy of the temporal arteries. Treatment is with prednisone 60 mg per day, which is gradually tapered to a maintenance dose of 10 mg continued for 1 to 2 years. The response is monitored with repeated ESR estimations.

APPROACH TO A PATIENT WITH LOW BACK PAIN

Low back pain is a common cause of discomfort in the adult population. Approximately 10 per cent of adults have experienced an attack at some time in their lives. In some of these patients the pain arises from pressure on a neurological structure (root, plexus or cord) and can be accompanied by motor weakness and sensory impairment.

The causes of low back pain are as follows:

1. **Congenital**: Lumbar canal stenosis; rarely spondylolisthesis[1]
2. **Traumatic**: Lumbosacral strain; vertebral fractures (always look for osteoporosis, metastases); protrusion of the lumbar intervertebral disc
3. **Infections**: tuberculosis (cold abscess); epidural abscess
4. **Arthritis**: osteoarthrosis; ankylosing spondylitis; Reiter syndrome; psoriatic arthritis; inflammatory bowel disease
5. **Neoplastic**: metastases (from lung, prostate, breast, others); multiple myeloma; lymphoma
6. **Miscellaneous**: articular facet syndrome, lumbar adhesive arachnoiditis[2]
7. **Referred pain**
8. **Postural pain**

Etiology and clinical features Five types of pain have been described: local, referred, radicular, postural and back pain due to spinal stenosis. *Local pain* is caused by disease or injury to any single part of the osseoligamentous vertebral column. Examples include cortical fractures of the vertebrae and ligamentous tears. There is a well-localised pain over the site of injury with tenderness on firm pressure or percussion. Pain is usually constant and there may be reflex splinting by the paravertebral muscles at the affected segmental level. The spasm of these muscles can be felt on palpation. To correctly diagnose the involved structure requires a good understanding of the surface anatomy of the region.

Referred pain is of two types: one which is projected from the spine to the viscera and another, more common, which is projected from the pelvic and abdominal viscera onto the spine. Causes of referred back pain include menstrual pain, renal colic, pelvic endometriosis, retroperitoneal tumours, pancreatitis and colitis. Upper abdominal diseases cause referred pain in the T8–L2 distribution, lower abdominal diseases in the lumbar region and pelvic problems are referred to the sacral spine. Visceral pain is usually unaffected by movement of the spine, does not improve on lying down and may be altered by visceral activity; pain in the bladder worsens during micturition.

Radicular pain (also called *root pain*) is secondary to the compression or stretching of a spinal root. The first sacral root (S1) is affected most often. Pain begins centrally and radiates distally along the sensory distribution of the affected nerve root. Coughing, sneezing, and straining while passing stools, are all factors which exacerbate radicular pain. Pain can also be elicited by maneuvers which stretch the affected nerve root. This type of pain may be accompanied by neurological deficit (motor, sensory or reflex) in the distribution of the nerve root.

Bad posture is probably the most common cause of persistent back pain. There is a normal lumbar lordosis. Sitting on soft surfaces (such as a low sofa) or bending forward (as when mopping the floor) tend to flatten the lumbar arch. Other factors such as wearing high-heeled shoes can lead to exaggerated lordosis. Having slightly unequal leg lengths (congenital or secondary to an old fracture) can lead to lumbar scoliosis. This abnormal curvature can strain the spinal ligaments and result in back pain. The most common causes of poor posture are obesity, and weakening of pelvic ligaments in multiparous women.

Back pain due to *spinal stenosis* is typically seen in older adults with osteoarthritic changes at multiple levels along the vertebral column. Often such individuals have a congenitally narrow spinal canal to begin with. When there is further narrowing due to mild disc prolapse or facet joint hypertrophy (which obliterates the

[1] Upper vertebra, usually L5, slips forward relative to lower vertebra

[2] Usually the consequence of multiple invasive procedures such as myelograms and surgery. There is persistent back pain, multiple patchy neurologic deficits and no satisfactory treatment. Spinal arachnoiditis may also occur as a sequel to tuberculous meningitis.

lateral spinal recess), there remains little space between the nerve structures (spinal cord and nerve roots) and their osseoligamentous sheaths. Prolonged activity results in transient increases in bloodflow and some swelling of the nerve structures. As a result there is a characteristic clinical syndrome which has been described as *neurogenic claudication.*

The differences between intermittent claudication and neurospinous claudication are given in Table 9.3.

Table 9.3

Intermittent claudication	*Neurospinous (Neurogenic) claudication*
Definite threshold (claudication distance)	No fixed threshold
Relieved by brief rest	Requires prolonged rest
Peripheral pulses are usually diminished or absent	Weakness or absent tendon reflex may be seen on examination, at rest or by examining after exertion

Examination of the lower back includes inspection of the spinal curvature; there is normally a dorsal kyphosis and lumbar lordosis. Presence of a 'gibbus' (a sudden, sharp angulation) indicates an abnormality at that site. Lateral curvature (scoliosis) may become more prominent when the patient is asked to bend forward. The range of motion in flexion, extension and sideways bending should be noted. Percussion of the spinous processes and palpation of the paraspinal musculature may help in localisation. A lesion of the S1 nerve root results in a positive *straight leg raising (SLR) test.* The patient is asked to lie down in a supine posture. Keeping the leg extended at the knee, the lower limb is passively raised until pain occurs. Usually flexion upto 80 degrees, at the hip, is possible without pain. If the pain is due to inflammation of the hip joint, external rotation of the thigh at the hip results in pain. Hyperextension is tested with the patient lying prone. A lesion involving the third or fourth lumbar roots may limit extension (Table 9.4).

Management Back injury may be prevented by avoiding obesity, keeping abdominal and vertebral muscles in optimal condition with regular exercise, maintaining a good posture while sitting and standing and providing adequate support to the spine while sleeping (by using a firm mattress or board). While lifting objects one should bend at the knees and hold the object close to the body.

Muscular strains and minor disc prolapses usually respond to conservative therapy. This involves rest till the acute pain subsides along with antiinflammatory analgesics such as ibuprofen (400 mg three times a day) or naproxen (375 mg twice a day).

In more persistent or chronic pain investigations which may be indicated include :
1. blood tests to rule out a systemic cause– total leucocyte count, erythrocyte sedimentation rate, calcium, phosphate and alkaline phosphatase;
2. plain X-rays of the lumbar spine, CT scan to evaluate the bone, CT myelogram to evaluate

Table 9.4 Localisation of nerve root compression

Nerve root affected	*Muscle weakness*	*Tendon reflex diminished*	*Impaired sensation*
L4	extension at knee; dorsiflexion at ankle	knee jerk	medial surface of leg below knee
L5	flexion at knee; inversion of foot; dorsiflexion of great toe	—	lateral surface of leg and dorsum of foot
S1	plantar flexion at ankle	ankle jerk	lateral border and sole of foot

the possibility of spinal cord or spinal root compression and, if possible, an MRI of the spine. The advantage of an MRI of the lumbar spine is that it may eliminate the need for an invasive myelogram;
3. if a specific root lesion is suspected based on the neurologic examination, an EMG may help to confirm this diagnosis.

These investigations should only be done if the clinical diagnosis is uncertain or there is a reasonable chance that the management plan will be modified by these results. Surgical treatment of a lumbar disc prolapse is performed only if there is a significant neurologic deficit or pain that does not respond to conservative therapy. Surgery is always preceded by a CT myelogram or an MRI of the lumbar spine and often by an EMG. Procedures which are commonly used include microdiscectomy, discectomy, and laminectomy. Some specialised pain clinics use injections of local anesthetics or corticosteroids administered adjacent to the facet joint or into the epidural space. A repeat injection is usually required in a few months. The indication for these is chronic back pain without a surgically correctable lesion or a 'failed back' syndrome.[1]

APPROACH TO CORTICAL LOCALISATION

The Frontal Lobe

The frontal lobe may be divided into four functional areas. The posterolateral surface controls voluntary movement on the contralateral side (motor areas); the medial surface above the corpus callosum (cingulate gyrus and adjacent areas) is a part of the limbic system; the area around the frontal pole is the prefrontal or frontal association cortex controlling judgement, motivation and personality, and the frontal periinsular area (continuous with the motor area of the face) regulates the motor aspects of speech.

1 'Failed back' syndrome refers to the persistence or recurrence of back pain following surgery.

The motor area consists of the precentral gyrus (area 4) which is the primary motor cortex and the area anterior to it (area 6) which is the supplementary motor cortex. Lesions in these two areas cause contralateral spastic hemiplegia as described in the first section under 'Approach to hemiplegia'. Anterior to area 6 is area 8, which controls movement of the head and eyes to the opposite side.

Lesions of the prefrontal areas cause a lack of initiative (*abulia* or *hypobulia*) and an inability to carry out complex sequential tasks. There may be a decreased appreciation of the consequences of an action (social disinhibition) and decreased insight into one's problems. Depression or inappropriate jocularity may be seen.

Lesions affecting the frontal deep white matter bilaterally (such as hydrocephalus) cause a characteristic disturbance of gait, urinary incontinence, disinhibition of 'frontal' *release reflexes* and dementia. The patient walks with a broad base using slow, small, shuffling steps and keeping his feet glued to the ground (magnetic gait, *Brun's ataxia* or *gait apraxia*). The following are the commonly elicited frontal reflexes: if the area around the lips is stroked, the lips pout (snout reflex); if the lips themselves are stroked, there are sucking movements (suck response). If the palm of the hand is lightly stroked, the patient's hand grasps the stroking object (grasp reflex); if an attempt is then made to gently retract the object, the patient's hand follows the path of the object for some distance rather than release it (*following response*). If the area over the glabella (between the eyebrows) is lightly tapped, the eyelids normally blink. Sustained tapping results in habituation and this response is lost. In patients with frontal lobe (or extrapyramidal) dysfunction, habituation does not occur and they continue to blink as long as the tapping is sustained; this is the positive *Myerson's sign*. The Babinski response is elicited and this has been discussed earlier.

Lesions of the frontal periinsular area (Broca's area, areas 44 and 45) in the dominant hemisphere cause a motor aphasia called Broca's aphasia. Lesions affecting the non-dominant hemisphere in the same area cause problems in prosody, that is, melodic intonation of speech.

The Parietal Lobe

The parietal lobe can be divided into three areas —the postcentral gyrus, the superior parietal lobule and the inferior parietal lobule. The postcentral gyrus (areas 3, 1 and 2) constitutes the primary somatosensory cortex and receives somatosensory input (touch, pain, temperature, pressure and vibration) from the opposite half of the body. Damage to this area does not affect the patient's ability to detect or localise these sensations. However, the ability to recognise an object by touch alone and to discern its shape, size, texture and weight, is impaired. This ability is called stereognosis and its loss results in *astereognosia.* Other abilities lost include the ability to perceive a pattern drawn on the hand (*graphesthesia*) and the ability to reliably perceive two closely adjacent stimuli as separate (*two-point discrimination*); the distance at which two-point discrimination is possible is increased in the affected limb.

The superior parietal lobule (areas 5 and 7) coordinates visual input and oculomotor control and uses both to generate an internal awareness of what the world looks like. Bilateral damage (usually due to watershed infarcts along the middle cerebral–posterior cerebral junction) leads to a syndrome called *Balint syndrome,* which consists of an inability to voluntarily redirect one's gaze to a given object (*ocular apraxia*), difficulty with hand-eye coordination as is required, for example, in threading a needle (*optic ataxia*), and difficulty in perceiving the visual field in its entirety; for instance a patient looking at a painting of a beach scene may be able to see the boats or the people onshore but not both at the same time (*simultanagnosia*). A unilateral lesion of the superior parietal lobule causes optic ataxia and transient abnormalities of pursuit movements to the contralateral side.

The inferior parietal lobule consists of the angular and supramarginal gyri (areas 39 and 40).[1] On the dominant side, the inferior parietal lobule aids in the representation of *intrapersonal* space. A lesion of the dominant supramarginal gyrus causes *conduction aphasia.* A lesion of the dominant angular gyrus causes *Gerstmann syndrome* characterised by *alexia* (inability to read), *agraphia* (inability to write), *acalculia* (loss of arithmetic skills), *finger agnosia* (inability to name individual fingers) and *right-left disorientation.* There may also be *constructional apraxia* (inability to copy drawings and make three-dimensional constructions). There may be apraxia of other activities such as dressing.

On the non-dominant side, the parietal cortices aid in the representation of *extrapersonal* space (the space beyond arm's reach). Lesions in this area cause a neglect of contralateral hemispace. While reading a patient may not notice words on the left hand page. When asked to write, she may use the right hand corner rather than the whole sheet. Sensitive tests include asking a patient to bisect a line into two equal halves or asking her to cross out all the stars scattered on a page amidst distracting stimuli. Such patients may bump into obstacles on the left. The ability to follow a previously known route or to learn a new route may be compromised. In extreme cases the patient may not recognise her own limbs on the contralateral side (*anosognosia* or *autotopognosia*) as belonging to her. Thus, a hemiparetic patient may deny having hemiparesis and when shown his own hand state that it belongs to the examiner.

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[1] The angular gyrus is the portion of the parietal lobe over the end of the superior temporal gyrus; the supramarginal gyrus overlies the terminal portion of the sylvian fissure.

The Temporal Lobe

The temporal lobe may be broadly divided into a medial portion mediating memory and effect, a lateral portion which participates in language and higher order visual associations, and the insula, which contains the primary auditory cortex (areas 41 and 42). The superior temporal gyrus on the lateral surface serves as the auditory association cortex (area 22).

Each auditory cortex receives information from both ears so that a unilateral temporal lobe lesion does not cause deafness. A lesion involving the auditory cortex bilaterally causes *auditory agnosia,* an inability to recognise specific sounds. The medial surface of the temporal lobe contains the structures of the limbic system (disorders of the limbic system are discussed separately). Disorders in this region impair memory and are discussed in detail in the section on disorders of memory. Lesions of the posterior part of the superior temporal gyrus (Wernicke's area) on the dominant side causes sensory aphasia (described in the section on language disorders). Lesions at the same location on the non-dominant side cause *amusia*– a difficulty in discerning the melodic and tonal qualities of music. Finally, bilateral lesions of the temporal pole cause a syndrome of apathy, amnesia, increased appetite, hyperorality (tendency to orally explore all objects) and hypersexuality. This syndrome is called the *Kluver-Bucy syndrome.* A partial syndrome may be seen following herpes simplex encephalitis, degenerative dementias and prolonged status epilepticus. Finally, a portion of the optic radiation curves around the temporal horn so that a structural lesion in this area can cause a contralateral *homonymous upper lateral quadrantanopsia.*

The Occipital Lobe

The occipital lobes are solely dedicated to visual processing. The primary visual cortex (area 17) lies on either side of the calcarine fissure and the visual information has a retinotopic organisation. The right half of the visual field is represented on the superior lip of the calcarine sulcus. Fibres from the macula project to the most caudal part of the calcarine region, bilaterally. Hence, a lesion confined to one occipital lobe causes a contralateral hemianopia but spares central vision in the affected half of the visual field. Bilateral lesions of this area cause blindness. Some patients may be unaware that they are blind (*Anton syndrome*). Lesions in the visual cortex may cause changes in the size and shape of objects which are seen (*metamorphopsia*).

Adjacent to area 17 are the visual association cortices (areas 18 and 19), where the visual information is processed according to shape, colour and movement and are recognised as meaningful objects. Damage to this area may cause *visual agnosia*[1] (inability to recognise objects seen). A lesion of the dominant visual association cortex can cause pure word blindness (the patient can see the words but cannot 'read' them) and colour anomia (inability to name colours although they can be matched).

APPROACH TO A PATIENT WITH HEMIPARESIS

The clinical approach to localising the lesion in a patient with hemiparesis is an excellent example of how anatomical information is used to understand and localise a variety of clinical lesions.

Descending motor pathways

The cortical control of voluntary motor activity is mediated by the so-called pyramidal system consisting of corticospinal and corticobulbar

[1] One variety of visual agnosia is prosopagnosia, in which the patient can identify an object as belonging to a generic class, for example as a face or as a car, but cannot recognise its specific characteristics, for example as a spouse's face or a friend's car. With a more severe lesion, there is visual object agnosia, where the patient can see the object but cannot recognise it even in a general way. The patient may be able to name the object if she can feel it.

fibres descending from the neurons (*Betz cells*) in the motor cortex to the lower motor neuron (which directly causes muscle contraction). An understanding of the anatomy of this system enables one to understand the motor disturbances in a variety of neurological syndromes.

The corticospinal and corticobulbar fibres also arise from premotor frontal areas and sensory areas in addition to the motor cortex. They descend through the *corona radiata* and the internal capsule (genu and posterior limb) to aggregate in the *crus cerebrum* on each side. They continue through the pontine tegmentum and at the rostral end of the medulla, come together to form the ventral *pyramids*. At the lower end of the medulla, the corticospinal fibres enter the substance of the medulla and cross over to the opposite side (*motor decussation*) to descend in the posterior part of the lateral funiculus of the spinal cord as the *lateral corticospinal tract* which terminates on the lower motor neuron.

Throughout their downward course, the corticospinal fibres retain a somatotopic organisation (fibres responsible for movement of adjacent body parts are close to each other). The somatotopic organisation of the motor cortex is shown in the Fig 9.8. In the internal capsule, the fibres to the face are the most anterior and those to the feet the most posterior.

A lesion restricted to the medullary pyramids will not cause loss of all voluntary movement. Instead, the fine tuning of voluntary movements as an exploratory activity in response to sensory stimuli is lost; for example, the delicate finger movements by which we explore and identify a

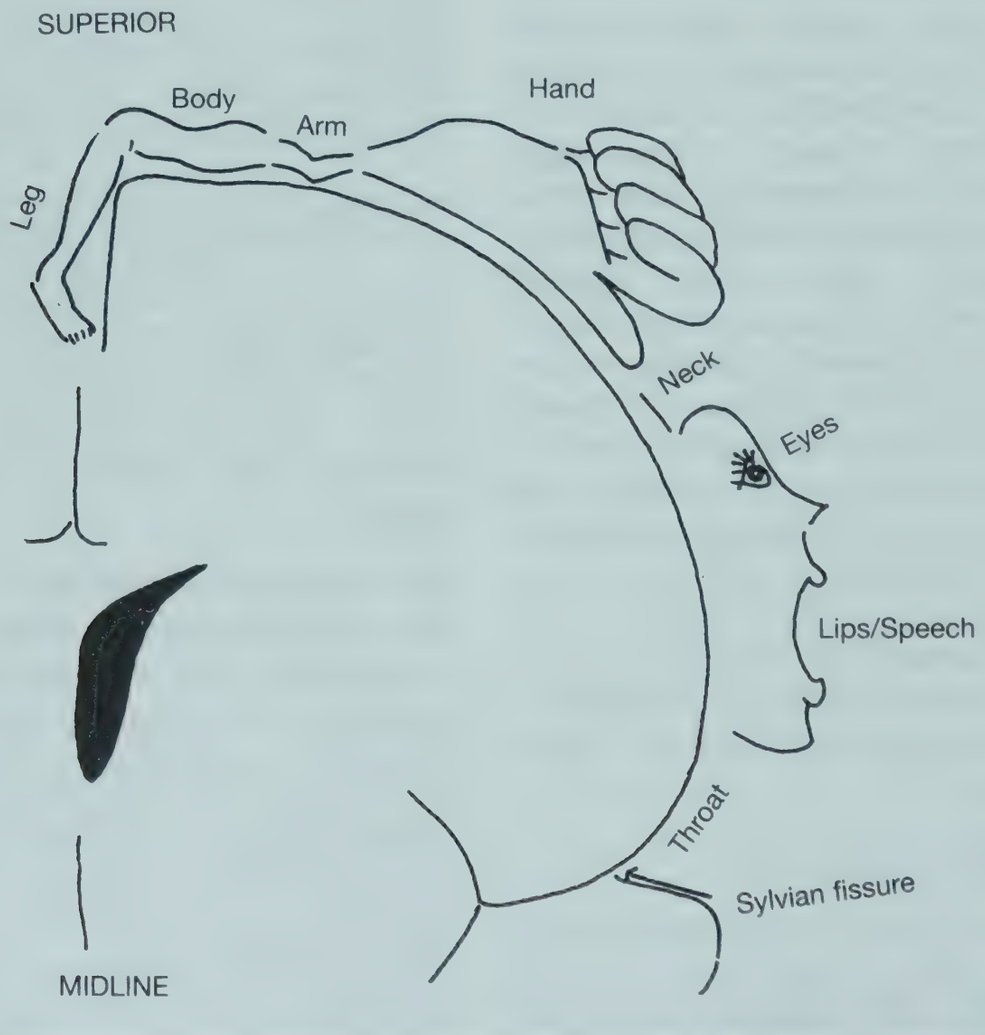

Fig 9.8 Cross-section through the motor cortex showing somatotopic organisation

star shape with our eyes closed. The clinical syndrome called a *pyramidal syndrome* is much more severe and results in paralysis. Obviously, fibres descending through other pathways are involved but these pathways are still unclear. With this proviso, in clinical parlance, 'pyramidal' refers to the system controlling voluntary movement and 'extrapyramidal' to the basal ganglionic functions of subconsciously maintaining posture and balance. Extrapyramidal pathways are discussed in the section on movement disorders.

Pyramidal Tract Syndrome

The common cause of a typical hemiparetic syndrome is a middle cerebal artery stroke involving the posterior limb of the internal capsule or the motor cortex. Immediately after the stroke, there is a period of flaccid paralysis, functionally analogous to spinal shock. After a few days, the tone and reflexes return and increase. Muscle tone is increased in a characteristic way (known as spasticity) so that when a muscle is stretched its resistance to stretch keeps increasing, upto a point when there is a sudden 'give' as the resistance abruptly decreases. This effect is called the 'clasp-knife' effect as it is similar to the resistance felt as one is trying to open a clasp-knife or pen-knife. It is thought that initially, sensory afferents in the muscle spindles are stimulated and these give a positive feedback to the alpha motor neurons increasing their rate of firing and hence the muscle tone. At some point, the afferents within the Golgi tendon organs are stimulated and these have a strong inhibitory feedback effect on the alpha motor neurons. The increased tone is maximal in the upper limb flexor muscles and lower limb extensor muscles.[1] Deep tendon reflexes become hyperactive. In extreme cases, clonus is seen. *Clonus* is a rapid series of rhythmic contractions (at least 4) seen when a muscle is suddenly stretched. It is typically looked for at the ankle (by sudden dorsiflexion) and in the hamstrings (called patellar clonus; this is elicited by extending the patient's leg, grasping the superolateral margins of the patella and rapidly moving it down towards the foot; approximately 1 cm of movement is possible).

As voluntary function returns, proximal muscles recover faster than distal muscles and movements of the fingers are the most severely and permanently affected. Movements requiring precision and skill recover less than coarser movements.

Localisation of level in hemiparesis A lesion in the cerebral cortex gives rise to cortical hemiparesis. The cortical localisation is easily recognised if there are associated seizures, aphasia, apraxia, agnosia or a cortical type of sensory loss (impairment of stereognosis and two-point discrimination). In the cortex, the motor fibres to the different parts of the body arise from a wide area; hence, lesions may affect only some of these fibres unless they are extremely large. Typically, therefore, a cortical hemiparesis affects one limb more than the other. Because the distal parts of the limb have the widest area of cortical representation, they are more likely to be affected. A lesion involving the paracentral lobule (meningioma, anterior cerebral artery infarct) affects the legs the most, the upper limb to a lesser extent, while the face is spared. With a lesion in the lateral prefrontal gyrus, the face is the worst affected, the upper limb less so and involvement of the lower limb may only be detected by a mild increase in the deep tendon reflexes or an upgoing plantar response. A lesion between these two areas will affect the upper limb to the greatest extent.

In the internal capsule, all descending motor fibres are close together. A lesion in this location is likely to affect the upper limbs, lower limbs, and face with equal severity. The medial margin of the posterior limb of the internal capsule lies adjacent to the posteroventral nucleus of the thalamus. Hence, capsular hemiparesis may be associated with thalamic sensory impairment

[1] A useful aid to memory is that the pattern is similar to what is seen in decorticate posturing.

(deep sensation impaired, later hyperpathia). An extension of the lesion posteriorly can cause homonymous hemianopia.

Brainstem hemiparesis (like capsular hemiparesis) involves the entire half of the body to the same extent. The presence of associated cranial nerve lesions on the side opposite to the hemiparesis (crossed hemiparesis)[1] localises the lesion to the brainstem. Facial paresis is a useful guide to localisation. Absence of facial weakness suggests a lesion below the pons. A lower motor neuron type of facial paresis on the side opposite the hemiparesis suggests a lesion within the pons. If there is simultaneous involvement of the sixth nerve on the same side as the facial nerve, this is called the *Millard-Gubler syndrome.* A lesion above the pons causes an upper motor neuron type of facial weakness on the same side as the hemiparesis. In the medulla, hemiparesis may be associated with paralysis and hemiatrophy of the tongue due to a hypoglossal nuclear lesion on the side opposite the hemiparesis (*medial medullary syndrome*). In the midbrain, paralysis of the oculomotor nerve on the side opposite the hemiparesis constitutes *Weber syndrome.* At the foramen magnum there may in rare cases be a syndrome of weakness in one upper limb and the opposite lower limb. This is called *cruciate hemiparesis* or double monoplegia. It is explained by the fact that the motor fibres to the upper and lower limbs decussate at different levels.

Hemiparesis which spares all the cranial musculature may be caused by a lesion in the lateral cervical spinal cord. Usually, however, there are at least a few signs on the contralateral side so that the syndrome becomes one of quadriparesis (weakness of all four limbs). Unilateral paralysis combined with a loss of vibration and position sense on the same side and loss of pain and temperature on the opposite side is called a *Brown-Sequard* syndrome. If the lesion in the cervical cord is below the C5 level, the weakness in the upper limb may spare some muscle groups based on their segmental innervation. Alternatively, there may be lower motor neuron signs at the level of the lesion; this localises the lesion. A lesion below T1 in the spinal cord cannot produce a hemiparesis. Rarely, a peripheral syndrome such as poliomyelitis may involve two ipsilateral limbs. Similarly, a lesion of the basal ganglia or cerebellum may be unilateral. In these cases, however, the weakness would not be of the pattern described above (the pyramidal syndrome) and, hence, should not be called hemiplegia.

Identifying the etiology of the hemiplegia The etiology of a lesion can be suspected from the pattern and site of the anatomical lesion and the time course of the illness. A neurological lesion like others in medicine may be due to a *congenital, traumatic, vascular, inflammatory, infective, neoplastic* or *degenerative cause* or *result from a functional disturbance.* A congential hemiparesis or one that develops in the first three years of life is called infantile hemiplegia. Causes include perinatal trauma and prematurity. The affected limbs are shorter than on the normal side. This is not seen with adult onset hemiparesis. Longstanding hemiparesis can be associated with ipsilateral dystonia. Trauma can cause hemiparesis due to pressure from a subdural or extradural hematoma, from a local contusion of brain parenchyma or from arterial injury such as a carotid dissection. The important clue is the temporal relationship between the trauma and the hemiparesis. Vascular causes include the two types of stroke–ischemic and hemorrhagic. The vital clue is the sudden onset and, in the case of an infarct, the distribution of the deficit in conformity with a known vascular territory. Inflammatory causes include multiple sclerosis (recurrent episodes) and the collagen vascular diseases (associated

[1] Ipsilateral hemiparesis with contralateral cranial nerve paresis may be due to two separate lesions; for example, meningitis may cause a cranial nerve palsy and an infarct; herniation or raised intracranial pressure can cause third or sixth nerve lesions as 'false localising signs'.

systemic symptoms). Infections such as meningitis (resulting in infarction), encephalitis, brain abscess, tuberculoma and subdural empyema can cause hemiparesis. The associated symptoms of headache, fever and, if present, neck stiffness suggest the diagnosis. Hypoglycemia is a metabolic problem that may present with hemiplegia usually in association with sweating and altered sensorium. Transient disturbances of function may result in transient hemiparesis following a seizure (postictal palsy), as a prodrome of a migraine headache or due to reversible ischemia (TIA). A special type of recurrent hemiparesis in children lasting for a few days at a time and alternately affecting the two sides is called alternating hemiplegia: the pathophysiology is not yet fully explained.

APPROACH TO SLEEP DISORDERS

Disturbed sleep during the night or excessive sleepiness during the day are very common complaints experienced at some time by almost every adult, and in a persistent fashion by a third.

Physiology of sleep The requirement for sleep varies with age, from 16 hours in a newborn to about 6 hours at the age of 60. An average adult sleeps 8 hours at night. Sleep is characterised into different stages based on how easily a person can be aroused, EEG activity, muscle tone, and presence or absence of eye movements. For clinical purposes, staging is done with the help of a sleep study or a polysomnograph.

Polysomnography (PSG) In this procedure, also called a sleep study, there is simultaneous recording of brain wave activity, cardiorespiratory events and muscle activity. There are one to three channels recording EEG (electroencephalographic) activity, two recording eye movements, two recording muscle activity (EMG) from the chin and leg respectively, one recording nasobuccal airflow, two recording movements of the chest and abdomen respectively, one recording blood oxygen saturation as recorded by an ear oximeter and an ECG (electrocardiographic) channel. The study period is approximately 8 hours, so the speed of recording is slower than in a standard EEG. A 30-second period is called an epoch. The recording may be combined with a video or the technician may manually record, decubitus (prone, supine or lateral position), snoring, seizures or other significant events. After the recording has been made, it is studied epoch by epoch and details of each are summarised in a hypnograph (Fig 9.9) which records the sleep state, apneic events, arousals and leg movements. After reviewing the hypnograph, a summary report is made as to how well the patient slept and whether or not any sleep-related disorder is present.

Stages of sleep

Sleep comprises two physiologically distinct states known as *rapid eye movement* (REM) sleep and *non-REM* sleep. Non-REM sleep is made up of four stages. Stage 1 is drowsy phase which is the transition from wakefulness. On the PSG, the EEG alpha pattern is replaced by a low amplitude, mixed frequency pattern with predominance of theta frequencies. The EMG shows a decrease in muscle tone and there are slow rolling eye movements. Stage 2 sleep is characterised by an EEG appearance of *sleep spindles* and K-complexes. *K-complex* is seen on the EEG as a large, slow, upward deflection followed immediately by a downward deflection. It is typically followed by a spindle, which is a $\frac{1}{2}$ to 2 second burst of regular 12–14 Hz discharges which wax and then wane in amplitude. This up and down pattern causes the spindle shape. Stages 3 and 4 are called *slow wave sleep* or deep sleep and are characterised by synchronised high amplitude delta waves.

REM sleep is the stage during which most dreaming occurs. The EEG looks like Stage 1 sleep but there are regular eye movements. Muscle tone becomes extremely low. REM sleep begins from and ends in Stage 2 sleep.

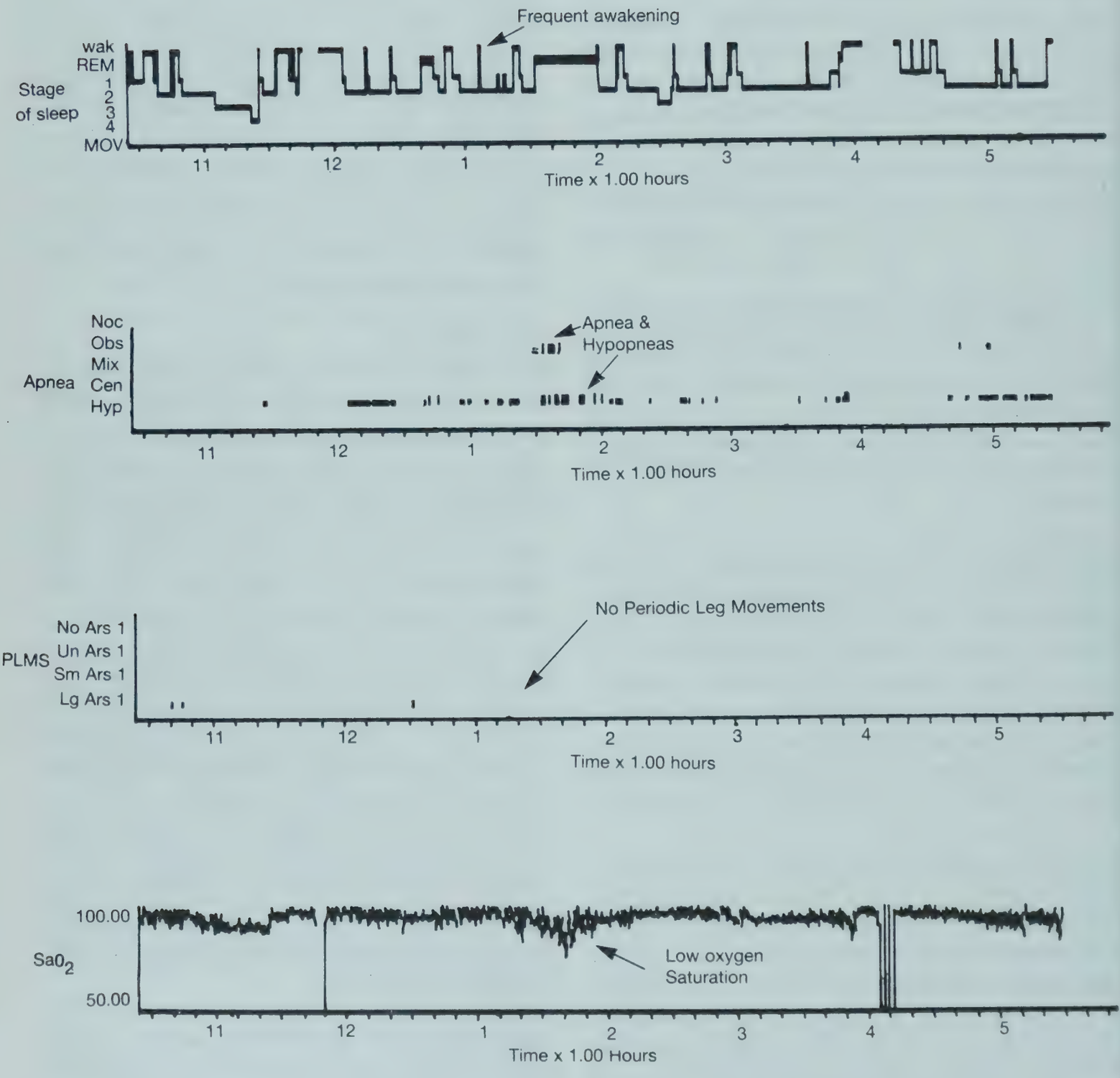

Fig 9.9 Hypnograph in a patient with sleep apnea

During a typical night, a person falls asleep and progresses through the various stages of non-REM sleep and then about 90 minutes later she has the first episode of REM sleep. There are 4–5 such cycles in a night. Each successive REM episode becomes longer. Each phase of sleep is characterised by disorders specific to that phase.

Sleep-related Symptoms

Insomnia

The most common sleep-related complaint is insomnia or inadequate sleep. This may be divided into difficulty with sleep onset, sleep maintenance or premature awakening. Common causes of insomnia are poor sleep hygiene and disturbances in the diurnal rhythm. Sleep hygiene includes such details as whether the patient sleeps at a regular time and avoids physical stimuli and mental stress at the time of sleep. People who work in changing shifts or frequently fly long distances may have sleep disturbances. The latter problem is commonly known as 'jet lag'. Overuse of caffeine, alcohol abuse as well as chronic abuse of hypnotics can all result in insomnia.

Patients who have difficulty with sleep onset may suffer from periodic leg movement disorder which is described below. Patients who can fall asleep but cannot stay asleep or those who sleep for 8–9 hours but awaken feeling tired may have a sleep apnea syndrome. Premature awakening is common in depression. PSG abnormalities in depressed patients include an early onset of REM sleep and an increased duration of the first REM cycle.

Insomnia should be managed by correcting reversible factors. Sometimes a patient who perceives himself as chronically sleep- deprived may actually be sleeping sufficiently. Documentation of this fact may be sufficient to reassure the patient. Hypnotics may be prescribed for transient stressful situations but should rarely be prescribed for habitual use. Commonly used agents are benzodiazepines, barbiturates and chloral hydrate. All these agents are addicting.

Hypersomnia

Two causes of excessive day time sleepiness are inadequate sleep at night (which may be due to sleep apnea) and the syndrome of *narcolepsy.* Narcolepsy is a syndrome characterised by episodic uncontrollable daytime sleepiness, *cataplexy* (the sudden loss of muscle tone often elicited by a strong emotion and involving the whole body or just one body part) and *hypnagogic* (while going to sleep) hallucinations. On a PSG there are characteristic abnormalities of REM sleep.

Narcolepsy is an inherited disorder strongly correlated with the HLA type DR2. The incidence of the disease is approximately 1 in 100,000. The onset of symptoms is between the ages of 10 to 50 years. The patient may have difficulty at school, at work or may be involved in an accident while driving. One or more daytime naps of 15–30 minutes will relieve the patient for 2 to 3 hours and patients often learn to do this on their own. The diagnostic test is a *multiple sleep latency test.* The patient is asked to have a nap in the sleep laboratory. If REM sleep occurs within 20 minutes of sleep onset, narcolepsy is diagnosed. Patients have been misdiagnosed as having complex partial seizures because of hallucinations, memory lapses and 'automatic' behaviour. If strategic napping is not sufficient to relieve the symptoms, methyl-phenidate, amphetamine, protriptyline and pemaline have been used. Amphetamine is the cheapest medication but has a high potential for abuse. Tricyclic antidepressants prevent cataplectic episodes.

Snoring

Snoring in sleep, if transient, is not serious. Persistent snoring associated with daytime tiredness may be a symptom of sleep apnea syndrome. However, about two-thirds of snorers do not have a sleep apnea syndrome. In these cases, taking care to sleep on the side and weight loss may stop the snoring.

Sleep apnea syndrome

Sleep apnea syndrome is characterised by episodes of respiratory dysfunction during sleep. Since the brain does not get sufficient oxygen, the patient wakes transiently and respiration improves. This pattern is repeated hundreds of times each night. Apnea is defined as complete cessation of nasobuccal airflow for at least 10 seconds. *Hypopnea* is defined as a 50 per cent or greater decrease in ventilation as compared to the awake state. Apnea is defined as central when there is an absence of ventilatory effort during the period of apnea. It is called *obstructive* when there is normal or increased respiratory effort (rhythmic movements of chest wall and diaphragm) but no airflow. A *mixed* apnea begins as a central event but once respiratory effort begins there is still no airflow indicating that there is an additional element of obstruction. A diagnosis of sleep apnea is made when there are at least six episodes of apnea or hypopnea in one hour, when the patient's sleep is significantly fragmented by arousals and the arterial oxygen saturation falls by more than 2 per cent.

Patients with obstructive sleep apnea are usually obese with small retrognathic mandibles. There may be enlargement of the tonsils and a swollen uvula which is probably secondary to the apneic episodes. When the patient sleeps, the tongue falls back as muscle tone decreases. Hence, apneic episodes are most frequent in REM sleep and in the supine posture. Failure to recognise this condition shortens the lifespan of the patient. There is a high incidence of cardiopulmonary complications and sudden cardiac death. Besides this, treatment can improve the patient's daytime function. The diagnosis should be considered in obese patients who present with any of the above symptoms or headaches. Treatment consists of weight loss, tonsillectomy, laser-assisted uvuloplasty, and failing these, a bedside machine which provides continuous positive airway pressure (CPAP) of 2–12 cm of water whenever the patient sleeps. This can result in complete resolution of symptoms. Central sleep apnea is commonly secondary to a neurologic lesion in the brainstem and is more difficult to treat. Progesterone and protriptyline have been tried as respiratory stimulants. A severe form of sleep-induced central apnea is called *Ondine's curse* and is managed with artificial ventilation whenever the patient sleeps.

Periodic leg movements

Periodic leg movements or nocturnal myoclonus are stereotyped rhythmic leg movements recurring every 20–40 seconds during Stages 1 and 2 of sleep. There is an associated feeling of restlessness and transient arousal. It is common is elderly patients. Clonazepam and levodopa are used as treatment options. Since many normal people have a few nocturnal leg movements, and since this condition is an evolving syndrome, confirmation of diagnosis and management are best left to a specialist.

Parasomnias

Parasomnias are behavioural disorders occurring in sleep. They do not result in daytime problems. Typically these are seen in children and adolescents. They include sleepwalking (*somnambulism*), *sleep terrors* (patient sits up and acts terrified but on awakening has no recall of the episode), *bruxism* (teeth grinding) and *enuresis* (bed wetting). No effective treatment is available for any of the parasomnias; patients typically outgrow them.

APPROACH TO A PATIENT WITH ALTERED SENSORIUM AND COMA

Consciousness is the awareness of oneself and the environment. The converse is the state of *unconsciousness* (coma) wherein the patient is unaware of most external stimuli. This state differs from sleep in that an unconscious person is not arousable while a sleeping person can be aroused with appropriate non-noxious stimuli. States between full wakefulness and

unconsciousness have been defined as lethargy, obtundation, and stupor. However, these transitional stages mean different things to different people, and therefore it is better to specifically describe the patient's reactions to external stimuli, the presence and nature of spontaneous movements and the respiratory pattern to categorise a patient's level of consciousness.

Anatomy of coma Coma results from an absence of cerebral hemispheric activities either because of diffuse, bilateral cerebral hemispheric dysfunction or because the involvement of the ascending reticular activating system (*ARAS*) in the midbrain and pons isolates the cerebral hemispheres from incoming stimuli. For this reason coma is unusual with unilateral cerebral hemisphere disease unless there is concomitant dysfunction of the other hemisphere or brainstem structures. A large unilateral hemispheric lesion may result in an elevation of intracranial pressure and displacement of intracranial contents past the fixed dural supports causing compression of other brain structures and, thus, result in coma. This phenomenon is called *herniation* and the various sites of herniation (uncal, tonsillar and subfacial) are shown in Fig 9.2. Diffuse metabolic processes can cause coma in the absence of a structural lesion.

Pathophysiology The pathophysiologic basis of coma is either the mechanical destruction of crucial brain areas as discussed above or generalised disruption of brain metabolism. The latter may be secondary to interruption of energy substrate delivery (hypoxia, ischemia, hypoglycemia, carbon monoxide poisoning) or alteration of neuronal biochemistry or membrane physiology (intoxication, epilepsy, concussion). The two mechanisms may coexist. An injured portion of the brain may release excitotoxins such as glutamate, or 'steal' blood supply, thereby impairing the function of an adjacent, structurally intact area.

Etiology Coma is not a disease entity but a syndrome reflecting a serious underlying disease process. The causes of coma can be divided into two main groups: 1) primary disease of the central nervous system, and 2) metabolic coma (Table 9.5).

Differential diagnosis Coma is a true medical emergency and the first priority should be to assess the patient to determine what measures need to be undertaken to maintain life and to prevent further deterioration if possible. An adequate airway must be established. Ventilation must be supplemented if necessary, intravenous access secured and intracranial pressure normalised. Once the patient is stable, a detailed history must be taken from all available sources. This may include actively seeking out (perhaps over the telephone) any individuals who may have pertinent information. Friends or family members are distraught and often do not realise the value of the information that they can offer; calm encouragement is invaluable. If the patient is alone, examination of his personal effects may offer clues. Some patients with diabetes, for instance, may carry a warning card. The history should include questions on the circumstances surrounding the loss of consciousness (rate of onset, associated symptoms), past medical history (diabetes, hypertension, epilepsy, heart disease), recent symptoms suggesting a space-occupying lesion (headache, vomiting, focal weakness) or infection (fever, personality changes) and evidence of poisoning. Suicidal patients have often spoken to someone hinting at the agent they may use. An empty bottle of an insecticide or prescription drug may have been found near the patient.

A screening general physical examination may reveal evidence of hepatic, renal, cardiac or respiratory failure. Hypertension may be secondary to an acute intracranial hemorrhage or may indicate hypertensive encephalopathy. Hypotension suggests shock, septicemia, poisoning or Addison's disease. Bradycardia

Table 9.5 Causes of coma

Primary CNS disease	*Systemic/Metabolic coma**
1. Meningitis	1. Cerebral malaria
2. Encephalitis	2. Typhoid encephalopathy
3. Brain abscess	3. Alcohol overdose
4. Brain tumour (primary or metastatic)	4. Poisoning (methyl alcohol, lead, barbiturates, carbon monoxide, etc.)
5. Infarction	5. Hepatic coma
6. Intracerebral hemorrhage	6. Uremic coma
7. Subarachnoid hemorrhage	7. Diabetic coma (ketoacidosis, hyperosmolar, hypoglycemic)
8. Intraventricular hemorrhage	8. Respiratory failure
9. Cerebral venous thromboses	9. Hypoxia
10. Closed head injury (concussion/contusion)	10. Hypertensive encephalopathy
11. Subdural hematoma	11. Hypo/hypernatremic coma
12. Epidural hematoma	12. Hypo/hyperthermic coma
13. Generalised seizures/postictal state	13. Endocrine coma (myxedema, Addison's disease, pituitary insufficiency)

* In most cases of metabolic coma, the patient has no localising signs.

may indicate a cardiac lesion or be secondary to raised intracranial tension of any cause. Hypothermia raises suspicion of myxedema coma and hyperthermia may suggest heat stroke, infection, or *datura* poisoning. The patient's breath may smell of alcohol, or acetone (diabetic ketoacidosis). Acidotic breathing suggests metabolic acidosis due to diabetic ketoacidosis, or uremia. The presence of skin petechiae suggests meningococcemia; rare causes include fulminant leukemia and thrombotic thrombocytopenic purpura. Cyanosis suggests hypoxia. Blistering of skin and mucosal membranes suggests barbiturate or opiate poisoning. Needle marks suggest diabetes or narcotic drug abuse. Assessment of the pupils is useful in suspecting certain drug toxicities (Table 9.6).

The examination of the patient should always include a search for evidence of head injury. Scalp lacerations, subgaleal hematomas and depressions in the cranial vault should be looked for. Other signs of head injury include discolouration of the mastoids (*Battle's sign*), bleeding from the ears or the nose, or periorbital discolouration, all of which indicate possible basal skull fracture.

If trauma to the cervical spine has been excluded, neck stiffness should be assessed. Presence of neck stiffness indicates irritation of the meninges by an infection or blood. Rarely, herniation through the foramen magnum can cause mild neck stiffness.

Technique of neurological examination in a comatose patient

Cranial nerves: In a patient with a decreased level of consciousness who is not yet comatose, a blink response to a visual threat (movement of hand towards patients's eye) is a crude indicator of intact vision in that half of the visual field. Fundus examination must be done and may reveal papilledema, retinal hemorrhages or subhyaloid hemorrhage (suggestive of subarachnoid hemorrhage).

Pupillary responses are very useful in localising the site of a structural lesion causing coma, and in differentiating between different drug-induced comas. Most non-drug causes of metabolic coma do not alter the pupillary response (Table 9.7).

Observation of eye position at rest and examination of extraocular pathways is also

Table 9.6 Drug-induced abnormalities in pupillary responses

Drug	*Pupillary response*
Opiates (Morphine, heroin)	Pinpoint, non-reactive
Glutethamide	Midposition, fixed
Atropine, datura poisoning	Dilated, fixed

Table 9.7 Localising value of the pupillary response in coma

Site of lesion	*Pupillary response*	*Explanation*
Bilateral hemispheric dysfunction	Bilateral small, reactive pupils	Sympathetic dysfunction at level of hypothalamus
Midbrain	Midposition (4 to 7 mm), unreactive	Tectal damage affects both the descending sympathetic fibres and the parasympathetic fibres arising from the Edinger-Westphal nucleus within the oculomotor complex
Pons	Pinpoint, reactive pupils. Magnifying glass may be required to see reaction	Damage to descending sympathetic tracts; parasympathetic fibres which exit at the midbrain level are intact
Tentorial herniation	Widely dilated fixed pupil (typically contralateral, may be ipsilateral)	Herniating temporal lobe crushes opposite oculomotor nerve against the edge of the dural notch; sympathetic fibres travelling with the V_1 branch of the trigeminal act unopposed

localising value. The eyelids may have to be manually elevated. Mild horizontal divergence of the eyes is normally observed in drowsiness. As the patient slips deeper into coma, the ocular axes become parallel again. An adducted eye at rest indicates a sixth cranial nerve lesion while an abducted eye with ipsilateral pupillary dilatation indicates a third cranial nerve lesion. These two nerves may be affected when there is raised intracranial tension of any cause (*false localising sign*). Vertical separation of the ocular axes (one eye higher than the other) or *skew deviation* results from pontine or cerebellar lesions. If the frontal gaze centre or its descending fibres are damaged, the opposite normal frontal centre acts alone and the eye will be pushed towards the same side as the damaged hemisphere (it will look towards the intracranial lesion, that is, away from the side of hemiparesis). A destructive hemipontine lesion will damage the pontine mechanism for ipsilateral horizontal gaze. The eyes, therefore, deviate to the opposite side (they look away from the intracranial lesion, that is, towards the side of paresis). Spontaneous eye movements in light coma consist of conjugate, horizontal roving movements. Their presence suggests that the midbrain and pons are intact. When there are no roving eye movements, the range of ocular movements may be tested using the

oculocephalic or the *oculovestibular* responses. The oculocephalic or *doll's eye response* is suppressed by fixation and, hence, is not seen in the waking state. Before testing, the integrity of the cervical spine must be established. (If cervical spine injury is suspected, the oculovestibular response is a better indicator.) While holding the eyelids open the head is moved briskly from side to side. The eye should move easily in a direction opposite to the direction of head turning. If the eyes stay 'locked' in place, this suggests pontine damage. Drug overdoses can cause a transient absence of the doll's eye response. The oculovestibular or caloric response is a stronger stimulus to reflex eye movements. The external auditory meatus is irrigated with at least 30 ml of ice-cold water injected rapidly. (Such testing would be extremely uncomfortable if the patient were awake!) An intact pontine response consists of tonic deviation of both eyes towards the side of irrigation. A patient who is comatose with subclinical seizures may show rhythmic jerky movements of the eye. Lesions of the superior tectal region (and hydrocephalus) cause a characteristic constellation of ocular signs called *Parinaud syndrome*. There is downward deviation of both eyes at rest, paralysis of spontaneous upward gaze, preserved pupillary light responses with loss of miosis during convergence, skew deviation and a special kind of nystagmus wherein the two eyes alternately converge and retract. The patient appears to be staring at his own nose.

Integrity of the fifth cranial nerve is tested by checking the corneal reflexes in patients who display spontaneous eye opening. Digital pressure over the supraorbital ridge is a painful stimulus and provokes a facial grimace. A unilateral seventh cranial nerve lesion will manifest as lack of movement of one half of the face during this maneuver. The gag response is assessed. If it is absent, this means that swallowing is likely to be impaired and airway protection is indicated.

Motor examination: The patient's posture while lying supine can provide clues to the site of lesion and the depth of coma. A lower extremity that is persistently externally rotated may be a clue to motor weakness. A lesion above the superior colliculus (at the level of the diencephalon) or severe bilateral cerebral hemispheric damage results in *decorticate posturing*. Briefly, this posture is due to increased flexor tone in the upper limbs and increased extensor tone in the lower limbs. There is adduction at the shoulder, flexion at the elbows and the wrist, with supination of the forearm, and the fingers are rolled into a fist. In the lower limbs, there is adduction, generalised extension, internal rotation and plantar flexion at the ankles. In a lesion localised to the midbrain, *decerebrate posturing* is seen. All four limbs are extended. The position of the lower limbs is similar to that in decorticate posturing. In the upper limbs there is adduction at the shoulder, *extension* at the elbow and hyperpronation of the forearm. The neck may show opisthotonic posturing. Both types of posturing may also be seen in metabolic coma, with decerebrate posturing indicating a deeper degree of coma and a worse prognosis.

Muscle tone should be assessed by passive movements. The muscle tone changes associated with decorticate and decerebrate states have been described above. Asymmetric flaccidity may be the only sign of hemiparesis. Lesions at the level of the lower pons or medulla cause flaccidity of all four limbs.

Comatose patients who make multiple spontaneous movements are in light coma. Involuntary movements due to seizures may manifest in a comatose patient with only small excursion, twitching of a foot, finger or facial muscle. Multifocal myoclonus may be seen in uremia, hypoxic encephalopathy, and Creutzfeldt-Jakob disease.

Response to sensory stimulation: It is important to assess the threshold at which a response is elicited and the nature of the response.

Asymmetry of response may indicate a focal lesion. Graded stimuli are presented starting with a loud voice calling out the patient's name or asking a simple question. If there is no response, this is followed by touch, a pinprick and finally pressure over bony prominences. The degree of pressure applied is increased gradually. The most painful stimuli are supra-orbital pressure and rubbing the examiner's fist over the patient's sternum. In light coma, the patient may be aroused transiently by the stimulus. Progressively increasing depth of coma is indicated by the sequential responses which follow, each indicating a greater depth of coma than the preceding response. These include groaning and a localising response (for instance, removing the examiner's hands), a specific flexor response (withdrawal of the stimulated limb), a generalised flexor response of all four limbs, generalised extensor (decerebrate) response, and finally a total lack of response to intensively painful stimuli.

Deep tendon reflexes should be examined to look for asymmetry.

Plantar responses: A unilateral upgoing plantar suggests a contralateral structural lesion. Bilateral upgoing planters may be seen with any type of coma.

Investigations Screening investigations include *blood counts, blood smear* (invaluable in detecting malarial parasite, leukemia), *blood biochemistry* (glucose, sodium, urea, creatinine, hepatic transaminase), and *arterial blood gases.* Simultaneously, a blood sample is drawn for drug screening. Rarely additional blood tests may be indicated– thyroid function, cortisol levels and antinuclear factor. A simple *urine* dipstick exam will pick up diabetic hyper-glycemia and proteinuria indicates renal damage. Additional urine tests are sometimes done to exclude lead poisoning and *porphyria. ECG* is taken to rule out myocardial infarction and cardiac arrhythmia (long strip of lead II). A *CT scan* of the brain can usually resolve doubts about the presence or absence of a space-occupying lesion. Usually, an initial non-contrast-enhanced CT is done which will detect any hemorrhage, and most tumours which are large enough to cause coma. Early infarction, bilateral subdural hematomas and mass lesions within the posterior fossa may cause only subtle CT abnormalities which may be overlooked. If these conditions need to be excluded, a contrast agent might be given immediately following the initial scan and a second CT (contrast CT, CECT) obtained. The contrast CT scan may also help in defining the nature of the mass lesion seen on the plain CT scan (differentiating between tuberculoma, abscess and tumour).[1] If meningitis is suspected, one must proceed with immediate lumbar puncture (within 30 minutes of presentation to the emergency). However, if the suspicion of meningitis is low, there are focal signs, and the patient is at a centre where CT scanning can be obtained rapidly, a negative CT scan provides strong reassurance that the lumbar puncture will not result in herniation. The conventional clinical indicator of raised intracranial pressure, that is, papilledema, may be absent if the elevation in pressure is of a short duration. A structural lesion in the temporal pole raises the possibility of herpes simplex encephalitis. A CSF picture of hemorrhagic lymphocytic pleocytosis makes the diagnosis highly probable. Finally, an EEG recording, even with only a few leads, can rapidly diagnose coma due to non-convulsive status epilepticus, a recently defined entity which is discussed in the section on seizures. Characteristic EEG abnormalities may also be seen in herpes encephalitis, the post-ictal state and hypoxic encephalopathy.

Prognosis The prognosis for recovery depends on the degree of coma and its etiology. Patients

[1] A tuberculoma typically shows ring enhancement of uniform thickness, an abscess shows ring enhancement with irregular or variable wall thickness, and a tumour shows irregular enhancement throughout the lesion.

with metabolic coma are more likely to make a complete recovery than those with a structural lesion. Among structural lesions, a lesion that impairs function without destroying the area (for instance, hemorrhage, edema) may be associated with a better functional recovery than a destructive lesion like an infarct or a tumour. The duration of the coma is also important. Coma lasting for more than 48 hours after cardiopulmonary resuscitation or coma of any etiology lasting for over a week is associated with a significantly worse prognosis. A constellation of signs indicating an extremely poor prognosis are absent pupillary responses, absent caloric responses and lack of spontaneous ventilatory effort. A patient who demonstrates these signs and continues to display them on retesting after 24 hours is said to be *brain dead.*

The Persistent Vegetative State

The vegetative state (coma vigil) is a condition wherein the patient shows no awareness of self or environment; however, sleep-wake cycles may be present and hypothalamic and brainstem autonomic functions are partially intact. If this state lasts continuously for at least a month, it is said to be persistent. The persistent vegetative state is not necessarily irreversible. The prognosis for recovery of consciousness is better in children. After twelve months in a persistent vegetative state (post-trauma) or even three months (non-traumatic), recovery of consciousness is very rare.

The Locked-in State

The locked-in state simulates coma but the patient is in fact conscious. The term 'locked-in' is used to describe a state of preserved consciousness associated with generalised muscular paralysis rendering the patient aware of sensations but unable to communicate. Such a state is associated with lesions of the pontine tegmetum which destroy all descending motor fibres. Vertical eye movements and blink responses are preserved. With patience on the part of the care giver, a system of communicating with the patient can be worked out. A similar syndrome may be seen in some cases of the Guillain-Barre syndrome or severe myasthenia gravis.

Brain Death

Brain death is defined as the irreversible loss of the clinical function of the brain, including the brainstem. To diagnose brain death there should be a known cause sufficient to explain severe brain damage and reversible causes (poisoning, drug intoxication and hypothermia) should have been excluded. The *three cardinal clinical signs of brain death are coma, absence of brainstem reflexes* (pupillary, doll's eye and caloric, corneal, gag) *and apnea.* Any patient who has spontaneous respiration is not brain dead. To perform an apnea test the patient on the ventilator is first stabilised (normal body temperature, blood pressure, blood gases and serum sodium; the patient should have recovered from spontaneous or induced neuromuscular paralysis) and then the ventilator is disconnected. If the PCO_2 rises to above 60 mm Hg, or 8 minutes elapse without the patient showing any respiratory movements, the apnea test is positive, suggesting brain death. A tracheal cannula may be used to deliver oxygen and the oxygen saturation should not be allowed to fall during the test. Otherwise there is a small risk that a salvageable patient may be rendered brain dead by the test!

In many countries brain death has been accepted as the equivalent of death defined by conventional criteria (irreversible cardio-respiratory arrest with fixed, dilated pupils). This permits futile life-support services to be discontinued. No patient who has been brain dead for over 24 hours (48 hours for pediatric patients) has recovered. Typically, despite continued life-support these patients die in 7–10 days of intractable hypotension and/or infections followed by cardiac arrest. If the diagnosis is made, the family should be told that the patient

is dead and then life-support may be discontinued. If the patient's organs are suitable for transplant, two physicians who are not part of the transplant team should certify brain death and the decision to discontinue life-support should be endorsed by the family before permission for removing organs is requested. Optional investigations which may be used to confirm the diagnosis of brain death include EEG (flat trace), brain scan (no uptake of isotope) and angiogram (total absence of cerebral flow).

Management The most important consideration in the management of coma is the maintenance of adequate life-support. Reversible causes should be corrected. In cases of intoxication, removal of the toxin by hemodialysis (barbiturates) or administration of an antidote (naloxone for opiates) is indicated. Uremic encephalopathy responds to dialysis and hypertensive encephalopathy to careful lowering of blood pressure. Infections, depending on the causative agent, should be listed; this includes the use of antibiotics for bacterial infections, antimalarials for cerebral malaria and acyclovir for herpes simplex encephalitis. Endocrine replacement (myxedema) and slow correction of hyponatremia should be undertaken where indicated. If the person is having persistent seizures, even if the magnitude of observed motor movements is small, aggressive treatment of seizures is indicated as this may result in improvement of sensorium. Surgery is indicated in cerebellar hemorrhage, and surgical debulking may reverse incipient uncal herniation in brain tumours.

If the coma is secondary to an elevation of intracranial pressure, measures to reduce intracranial pressure (intravenous mannitol, therapeutic hyperventilation, ventricular puncture, ventriculoperitonial shunting) should be instituted. If the raised intracranial pressure is due to cytotoxic brain edema (edema secondary to brain tumours or surgery) steroids are beneficial.

If the patient requires long term care, maintenance of nutrition and hydration is important. Intravenous fluids should not be hypotonic (5% dextrose should not be used) as this would worsen brain edema. Ryle's tube feeding or feeding gastrostomy are better choices for prolonged nutritional support than intravenous total parenteral nutrition. Repositioning the patient every 2–4 hours prevents the development of pressure sores. Prevention of infection includes scrupulous attention to asepsis in pulmonary care and the use of the condom catheter rather than an indwelling urinary catheter in male patients. To reduce the risk of aspiration the head end should be elevated by 30 degrees. Administration of antacids or H_2 receptor antagonists reduces the risk of stress ulcers (thereby, preventing gastric hemorrhage). Corneal abrasions are avoided by using methyl cellulose eyedrops and taping eyelids. Subcutaneous heparin at a dose of 5000 IU twice daily reduces the risk of deep venous thromboses and subsequent pulmonary embolism. As the patient gradually recovers, rehabilitation to prevent contractures, and to restore motor and cognitive function, should be undertaken.

KEY CONCEPTS

Headache

➢ A detailed history is critical; the frequency, associated symptoms, quality, location, and *duration-time-intensity* are helpful in making an etiologic diagnosis. The response to a particular medication is not diagnostic in itself. Hypertension usually does not cause headache unless diastolic blood pressure is ≥110 mm Hg.

- *Migraine*
  - Typically, it has an onset in childhood with an increase in frequency at puberty and at menopause.
  - The headache is frontotemporal in location, throbbing in character, and has a duration of a few hours to upto 2 days.
  - Migraine may be with (*classical*) or without (*common*) an aura (e.g., scintillating scotomata,) may be uni- or bilateral. It may be provoked by food, red wine, menses, oral contraceptives.
  - Migraine responds to aspirin, NSAIDs, ergot preparations or sumatriptan. Consider using β-blockers for prophylaxis if headaches are frequent and disabling.
- *Tension headaches*
  - Usually have a generalised location with a *band-like discomfort*; there is a slight female preponderance, and aspirin and paracetamol relieve the pain.
  - Coexisting anxiety or depression should be treated.
- *Cluster headaches*
  - These headaches have a lateral orbital or temporal location, occur periodically (e.g., daily for 6 weeks) and last for about 45 minutes. Headaches often occur at night and wake up the patient.
  - Onset is in middle age, men are more susceptible and alcohol may be a precipitating factor.
  - Headaches are associated with *redness of eyes, lacrimation, nasal congestion* and *rhinorrhea.*
  - Treatment choices include prednisone, ergotamine, sumatriptan and oxygen inhalation. Prophylaxis may be attempted with lithium, verapamil or methysergide.
- *Headaches associated with brain tumours*
  - These may be variable in character and *often interrupt sleep.*
  - The pain is monophasic, gradually worsening, and is accompanied by nausea and vomiting.
- *Headaches associated with subarachnoid hemorrhage*
  - Headache is of sudden onset and very severe. There may be transient dizziness or altered sensorium. Associated neck stiffness or ptosis is suggestive.
  - A non-contrast CT scan or CSF examination (showing xanthochromia) establishes the diagnosis. An early angiogram and surgical 'clipping' of the culprit berry aneurysm is recommended in the non-comatose patient.
- *Headache associated with infections*
  - Patients with headache and high fever should be examined for presence of meningitis, encephalitis or a brain abscess. An urgent CSF examination may be revealing (unless intracranial pressure is elevated, in which case a contrast-enhanced CT scan is preferred).
- *Giant cell arteritis*
  - The headache has a temporooccipital location and occurs typically in persons over the age of 55 years. Presence of *local scalp tenderness* (or tenderness over the temporal artery) is suggestive.
  - ESR is markedly elevated. Treatment with prednisone prevents potential visual loss.

Backache

- Backache may be one of five types: *local, referred, radicular, postural,* or *due to spinal stenosis.*
- A good history and physical examination provide clues to the likely etiology. The most common cause of backache is bad posture.
- *Local* pain arises from lesions of the vertebral body or joints. It may be sharp or dull. It varies with the position of the patient, and with certain movements. Examination may reveal reflex splinting by paravertebral muscles and the culprit area may be tender on percussion.
  - *Referred pain* is a deep aching pain from a visceral source. *Radicular pain* is due to nerve root irritation/compression; it is severe in intensity, radiates distally, corresponds to the territory of the nerve root, and increases on coughing or sneezing. There is pain on SLRT or on forward bending with knees extended when the S_1 root is affected.
  - *Postural* pain is a dull cramp-like pain which may be associated with tautness of the stressed muscle. *Spinal stenosis* causes *neurospinous claudication*; unlike intermittent claudication, there is no exertional threshold for onset of pain, relief requires prolonged rest, and there may be evidence of decreased deep tendon reflexes or weakness of muscles on examination after exertion.
  - An X-ray of the spine is helpful in excluding destructive lesions of the vertebra and may reveal osteophytes which have the potential for causing nerve root compression. When pain is severe and persistent, a CT scan or an MRI scan may be ordered; beware of incidental abnormalities on MRI that may not be causing the clinical symptoms.
- Treatment consists of simple measures such as maintaining good posture, regular exercise, weight reduction, and the use of a hard bed. Analgesics may be used for pain relief. Muscle relaxants have an adjunctive role. Occasionally surgery may be indicated: if there is compression of spinal nerve roots with neurologic deficit or if there is disabling pain due to spinal canal stenosis.

Lobar syndrome

- Remember that the *left* cerebral hemisphere is dominant (in a right-handed individual) and important for *language* and *auditory perception*, while the *right* hemisphere has a critical role in *visuospatial perception.*
- Frontal lobe lesions are characterised by reduced speech and motor activity (abulia), change in personality (disinhibition), slight reduction in intelligence, gait and stance abnormalities (wide-based gait with flexed posture), reduced verbal fluency (left) or visuospatial ability (right).
- Temporal lobe lesions manifest with defects in visual fields (upper homonymous quadrantonopsia), aphasia, auditory illusions, psychotic behaviour, and amnesic syndrome in bilateral lesions.
- Parietal lobe lesions are associated with the cortical type of sensory deficit, visual inattention, constructional apraxia, and in left sided lesions, alexia, agnosia, ideomotor apraxia and Gerstman's syndrome.
- Occipital lobe lesions can cause
  - contralateral homonymous hemianopsia, and in the case of dominant hemispheric lesions, agnosia and alexia.

Hemiplegia

- In order of frequency, causes include vascular lesions, trauma, brain tumours, demyelination and infections.
- A careful history and physical examination can establish an anatomic diagnosis in most cases.
- Lesions in the cortex or white matter of the internal capsule affect the face, the arms, and the legs on the opposite side. Seizures, speech defects, a cortical type of sensory loss (e.g., two-point discrimination) or visual field defects favour a cortical or subcortical location (as opposed to a capsular location)
- *Pure motor paralysis* is seen in lesions of the posterior limb of the internal capsule, cerebral peduncles, pons or the pyramids.
- *Crossed paralyses* (cranial nerves and face affected are on the side opposite the extremities involved) suggest a lesion in the brainstem.
- If cranial nerves or muscles innervated by them are spared, a high cervical cord lesion may be responsible; usually such a lesion causes bilateral signs.

Sleep apnea

- *Apnea* refers to cessation of airflow for ≥10 seconds during sleep resulting in hypoxemia. There is an association with the male sex and with obesity.
- Two types are described: *obstructive* (obstructive lesion at oropharynx with continued ventilatory effort) and central (CNS origin, ventilatory effort ceases).
- Obstructive sleep apnea is associated with daytime hypersomnolence. Central sleep apnea is associated with insomnia, frequent arousal. Complications of sleep apnea syndrome include pulmonary and systemic hypertension, arrhythmias and sudden death.
- Diagnosis is established with a sleep study (polysomnography).
- Management includes weight loss, correction of anatomical abnormality, CPAP.

Coma

- Coma is usually indicative of damage to either the *cerebral hemispheres* or the *brainstem reticular activating system*, or to both. A variety of metabolic, neurologic, systemic illnesses may manifest with coma.
- A detailed history (from attendants) and physical examination is vital for establishing an etiologic diagnosis. This includes assessment for the presence of fever, major organ dysfunction (liver, renal or respiratory failure), evidence of drug use/abuse or poisoning. Remember that the most common stroke (MCA territory) does not usually cause acute onset of coma.
- Evaluation of *brainstem reflexes* (pupillary light responses, eye movements, respiratory pattern) and for the *presence or absence of localising signs* is central to the diagnostic approach.
- *If brainstem reflexes are intact, and there is no lateralising finding*, consider:
  a. with normal CT scan: bilateral hemispheric dysfunction due to metabolic abnormality, hypertension, an encephalopathy, or acute demyelinating disease
  b. **with abnormal CT scan**: subdural hematoma, contusion, subarachnoid hemorrhage
- *if brainstem reflexes are intact but there are lateralising findings*, suspect:
  a. a unilateral mass lesion (hemorrhage, infarct, tumour, infection)
  b. asymmetric but bilateral dysfunction (postictal state, metabolic abnormalities)
- *if brainstem reflexes are abnormal*, suspect:
  a. an anatomic lesion in the brainstem (hemorrhage, tumour, trauma)
  b. brainstem dysfunction without mass lesion (drug overdose, encephalopathy)
- Important tests include routine investigations (blood urea, electrolytes, liver function tests, ABG, toxicologic screening), CT/MRI, EEG and CSF examination (when index of suspicion of meningitic illness is high).
- Management includes both *supportive* (airway patency, circulatory support, vascular access, care of the eyes, skin, bowel and bladder) and *specific* measures (e.g. lowering blood pressure in hypertensive encephalopathy, dialysis in renal failure).

9.3 Diagnostic methods for evaluation of the nervous system

Lumbar Puncture (LP)

The lumbar puncture or spinal tap is a relatively simple and useful test. It involves inserting a fine needle into the spinal subarachnoid space in the lumbar region in order to obtain a sample of the cerebrospinal fluid (CSF).

Technique Normally an 18 to 20 gauge needle is used. If raised intracranial pressure is suspected or if the patient has had severe post-LP headaches in the past, a finer needle (22–24G) is used. In difficult cases, a seated posture is used. A detailed discussion of the procedures is provided in Appendix A.

Utility This procedure enables one to measure the pressure within the subarachnoid space and analyse the composition of the CSF (biochemical, cytology and microbiology). The lumbar puncture may also be used to inject contrast material into the subarachnoid space (iophendylate, metrizamide, air for contrast myelography; radioactive iodinated serum albumin for investigating CSF rhinorrhea and for assessing CSF dynamics). A lumbar puncture may be therapeutic in patients with benign intracranial hypertension (where CSF is drained) and for the administration of spinal anesthetic agent and other intrathecal drugs (antimicrobials etc.).

Composition of CSF in health and disease The opening pressure of the CSF is measured using a saline-filled manometer. The normal pressure ranges from 95–165 mm of water with the patient in the lateral decubitus position. If the patient is seated, the CSF pressure may be up to 240 mm of water. If the opening pressure is greater than 400 mm water, one should rapidly complete the procedure and then administer mannitol (1 mg/kg over 30 minutes) as the risk of tonsillar herniation is high.

The gross appearance of the CSF is normally clear. If there are more than 200 cells/mm^3, the appearance is turbid. If the protein content is very high or if there has been bleeding into the CSF, the fluid may appear yellowish (*xanthochromia*) or frankly blood-stained. Blood-stained CSF is most commonly seen due to traumatic tap. This occurs when one of the veins in the vertebral plexus or within a paravertebral muscle is punctured and the blood is carried by the lumbar puncture needle into the subarachnoid space. If the amount of bleeding is small, the CSF may become clear while it is being collected in different tubes for the various investigations. If the blood in the tube clots, this is suggestive of a traumatic tap. A traumatic tap can be reliably differentiated from a subarachnoid hemorrhage only by immediately centrifuging the bloody CSF; xanthochromia in the supernatant (the result of bile pigments from erythrocytes) suggests subarachnoid hemorrhage.

A quantitative cell count is done on the CSF using a white blood cell counting chamber. Normally, there are less than 4 white blood cells/mm^3. The normal ratio of white blood cells

to erythrocytes in CSF is 1:700. Inflammation of the meninges causes a marked rise in the number of white blood cells. If the protein content is over 1000 mg/dl, a coagulum will form on the surface on standing the specimen; such a 'cobweb' may be seen in tubercular meningitis. A spinal block can result in CSF loculation and a rise in protein content within the loculated fluid (*Froin syndrome*). The CSF glucose content should be interpreted with reference to a simultaneously obtained blood glucose level. The CSF glucose should be over 40 mg/dl and is usually two-thirds of the blood glucose level. A low CSF glucose (*hypoglycorrachia*) is seen when actively metabolising microorganisms or inflammatory cells use up some of the glucose. A Gram stain of the CSF and India ink stain for cryptococcal yeasts should be performed if meningitis (acute or chronic) is suspected. Cytology using millipore filters may detect malignant cells. Serology, including tests for syphilis, may be useful. The CSF should be cultured for bacteria, mycobacteria, and fungi. Protein immunoelectrophoresis may show oligoclonal bands in multiple sclerosis, subacute sclerosing panencephalitis and neurosyphilis. CSF myelin basic protein is a marker of demyelination in multiple sclerosis.

Contraindications Raised intracranial tension, local infection of overlying skin (or underlying tissues) and a bleeding diathesis are contraindications to performing a spinal tap. In patients with spinal cord compression, a cisternal puncture or a lateral cervical puncture (C1–C2 level) are preferred. The altered CSF dynamics associated with a lumbar puncture can worsen the spinal cord compression.

NEUROIMAGING

Computerised Tomography

Computerised axial tomography (CAT or CT scan) became available in the 1970s and revolutionised neurological diagnosis. It is a sensitive, reproducible non-invasive technique which is often the diagnostic procedure of choice. Even when an MRI scan is available, the CT scan is more useful in two situations: firstly, in the emergency room, it is useful in evaluating acute head injury and spinal trauma, in distinguishing ischemic from hemorrhagic stroke, in detecting and locating an intracranial mass lesion, and combined with intrathecal injection of contrast (CT myelogram), in detecting and localising spinal cord compression. A plain CT is done and, if required, is followed by a contrast-enhanced CT scan. A plain scan is necessary initially because once contrast is administered it may not be possible to differentiate spontaneously hyperdense lesions (hemorrhage) and contrast-enhancing lesions (tumour). Contrast-enhancement is seen wherever there is a breakdown of the blood-brain barrier due to

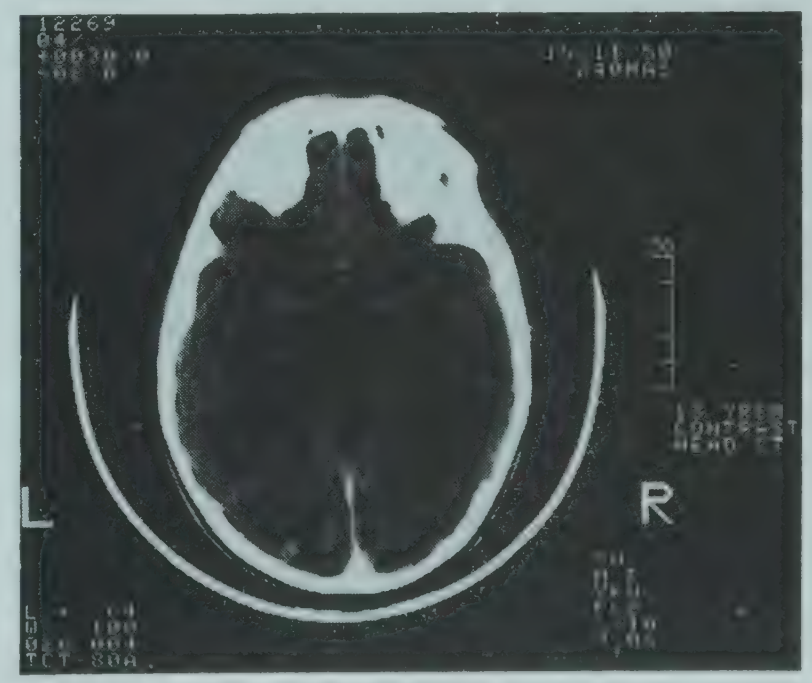

Fig 9.10 The single ring enhancing lesion shown in this CT scan is a common, puzzling problem for neurologists.

inflammation (chronic meningitis, tuberculoma), or tissue destruction (tumour) (Fig 9.10). In an acutely ill patient, a CT scan has the advantage over an MRI scan in being more rapid, less susceptible to movement artifacts, more easily available in most hospitals and in not interfering with the function of the life-support systems.[1]

The CT scan is better than the MRI in detecting an 'early' hemorrhage, intracranial calcification, fractures of the skull or spine and metastatic involvement of the skull.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI: also called nuclear magnetic resonance or NMR scan) became available in the 1980s and effected a second revolution in neurological imaging. Soft tissue contrast is better with MRI than any other imaging technique. Images can be obtained in any plane and blood vessels can be imaged without administration of contrast agents. The principles of MRI, its advantages and disadvantages have been discussed in the section on imaging in medical disorders. An additional disadvantage of the MRI, particularly in neurology, is that it can show incidental anatomic anomalies which can be misinterpreted as causing a patient's illness. Prominent examples are non-specific white matter changes seen in as many as 30 per cent of subjects over the age of 60 and incidental vertebral column changes, such as disc degeneration.

MRI has specific utility in the following situations: 1) imaging of the posterior fossa, 2) imaging of the spinal cord, 3) detection of demyelination, 4) screening for vascular malformations, 5) imaging of the pituitary fossa and the parasellar region, 6) investigating neurologic disorders in pregnant women, and 7) the presurgical work-up of a patient with intractable epilepsy.

In the posterior fossa, imaging with CT is hampered by bone and movement artifacts. Nevertheless, in an emergency situation, a non-contrast CT is as good as an MRI for detection of cerebral edema, hemorrhage or hydrocephalus severe enough to merit surgical intervention. MRI is better at detecting small infarcts within the brainstem and the extent of tumours in the cerebellopontine angle as well as congenital malformations (such as the Arnold-Chiari malformation).

In imaging the spinal cord, MRI has the advantage that the entire spinal cord and canal can be screened using a few sagittal sections. Thus, when screening for metastatic disease, MRI is more accurate than a bone scan. A CT needs to be done cross-sectionally at each suspected level, but shows a greater detail of bones. MRI is the preferred test for suspected herniated disc after a plain X-ray of the spine. It is particularly useful in postoperative patients, where scarring can be visualised. Because of the tissue scar, myelography may be difficult in these patients. For lesions within the substance of the spinal cord (*intramedullary lesions*), an MRI with paramagnetic contrast (gadolinium DTPA) is the most sensitive test and can differentiate between syringomyelia (non-enhancing) and an intramedullary tumour (enhancing).

Demyelinated areas in multiple sclerosis and leukodystrophies are best seen with an MRI. Using gadolinium contrast, one can differentiate new active lesions from old ones in a patient with multiple sclerosis. However, the presence of white matter changes on MRI should not lead to a diagnosis of multiple sclerosis in the absence of the characteristic clinical picture.

When patients or family members require screening for the presence of arteriovenous malformations or aneurysms, MRI along with magnetic resonance angiography (MRA) is preferred, as it is non-invasive. If the MRA is normal and the index of suspicion (for a vascular malformation) is high, conventional angiography (which remains the gold standard) may be performed.

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[1] The strong magnetic field of an MRI may interfere with life-support systems.

Pituitary microadenomas (<1 cm), lesions of the cavernous sinus and mesial temporal sclerosis (causing epilepsy) are better visualised with an MRI than a CT scan. Pregnant women should not be subjected to radiation or contrast injection. Therefore, in pregnant women a plain MRI is preferable to a CT scan.

Angiogram and Digital Subtraction Angiography

These have been discussed in the section 'Imaging in medical disorders'. An angiogram (conventional or digital) remains the gold standard if the vasculature is to be imaged before planning surgery on a carotid stenosis, an aneurysm, an arteriovenous malformation, venous anomaly or highly vascular tumour. Because an angiogram is invasive and associated with a definite though small risk, non-invasive ultrasound (Doppler) studies are preferred as screening tests for detecting carotid stenosis in the neck. For assessing flow in the intracranial portion of the internal carotid and the proximal middle cerebral artery, a specialised technique called **transcranial Doppler** may be used. In this technique a special low-frequency, high-intensity probe is used to enable insonation through bone. The images are obtained through the orbit, the thin bone over the temporal region or the foramen magnum (for the vertebral artery). Transcranial Doppler permits the estimation of flow velocities in intracranial vessels and the evaluation of collateral circulation. As a vessel narrows, the flow velocity of the blood increases. This fact is useful, for example, in patients with subarachnoid hemorrhage where repeated transcranial Doppler studies may detect early vasospasm.

Myelography

Myelography is a technique to image the contents of the vertebral canal (the spinal cord and its coverings) using X-rays. Following intrathecal injection of radioactive contrast material. images are obtained using either conventional radiography or computed tomography (*CT myelogram*). The contrast used is metrizamide, a water-soluble contrast agent that is spontaneously absorbed following the procedure. Unlike older water-soluble contrast media, it is relatively non-toxic even if some contrast enters the cranial subarachnoid space. Contrast media that are not water-soluble (iophendylate or Myodil), are less commonly used because 1) they will not permit CT evaluation, 2) the contrast has to be drained through the lumbar puncture needle (after the procedure), and 3) residual contrast may interfere with CT or MRI studies for years.

Conventional myelography produces good quality pictures but cannot show cross-sectional images and is a tedious procedure for the patient and the radiographer. After the dye is introduced, the patient is asked to assume different postures (prone, supine) and the table tilted to enable the contrast to navigate past the natural curves of the spinal cord and reach the required areas. A CT myelogram is preferred to an MRI in cervical disc disease and in patients who require metallic stabilisation devices (such as halo traction) or life-support systems (as in high cervical cord lesions). The potential complications of a myelogram are those of a lumbar puncture and those related to the injection of contrast into the epidural or subdural space instead of the subarachnoid space.

ELECTROPHYSIOLOGY

The Electroencephalogram (EEG)

The electroencephalogram (EEG) is a standard, non-invasive procedure for recording the summated electrical activity of the brain using electrodes positioned on the surface of the scalp. The electrodes are placed in standard positions as defined by a *'10-20'* system.[1] Eight to sixteen

[1] The '10-20' system is so called because the distance between electrodes is measured as 10% or 20% of the anteroposterior distance between the nasion on the frontal bone and the inion on the occipital bone.

amplifier channels record the voltage difference between pairs of electrodes as a graph of voltage on the Y-axis versus time on the X-axis. The recording may be made using sensitive ink pens on a paper moving at a standard speed of 3 cm/second.[1] The recording may also be digitally acquired to be displayed on a video monitor. Electrical activity in the frequency range 3–150 Hz and voltage range of 3–150 microvolts is recorded. The patterns seen on the EEG are defined by frequency and amplitude. In general, low frequency waves have a higher amplitude. The normal activity in a person who is awake but whose eyes are closed is called *alpha activity.* These waves are 9–11 Hz in frequency, have an amplitude of 30–50 microvolts and are best seen over the parieto-occipital regions. Openings of the eyes or focussed mental activity results in a decrease in alpha amplitude and synchrony (alpha attenuation). Other patterns of wave activity seen in the EEG are : 1) *beta* waves which have a frequency of 12–14 Hz and an amplitude of 10–20 microvolts. They may be seen intermittently over the frontal lobe. Excessive beta activity is seen in patients who are taking barbiturates or benzodiazepines; 2) *theta* waves which are slower than alpha waves (frequency 4–7 Hz) and have variable amplitude (20–100 microvolts). They occur normally in Stage 1 sleep (low-amplitude) and pathologically whenever the brain function is depressed (high amplitude diffuse slowing as in metabolic encephalopathy); 3) *delta* waves which have a frequency of 2–4 Hz and an amplitude of 50–350 microvolts. They are seen in slow wave sleep and overlying intracranial abnormalities such as tumours.

The neurological conditions in which the EEG may be useful are: 1) epilepsy, 2) diagnosis of Creutzfeldt-Jakob disease, subacute sclerosing panencephalitis and herpes simplex encephalitis, 3) intraoperative monitoring of brain function during cardiopulmonary bypass or carotid endarterectomy, 4) differential diagnosis in comatose patients and 5) detection of structural lesions.

The EEG is indispensable for the management of epilepsy and its utility here is discussed in the section on epilepsy. The EEG is abnormal in patients with intracranial space-occupying lesions, particularly if the lesion is large, supratentorial and has developed rapidly. With the advent of imaging techniques, however, the EEG is rarely used for this purpose. When used in these conditions, the abnormalities observed include asymmetry of background activity, focal slow waves or seizure discharges.

Special EEG techniques include ambulatory EEG, simultaneous ambulatory EEG and ECG (for evaluating syncope), simultaneous video and EEG recording using a split screen television monitor (video EEG), and recording from specially placed electrodes which may be on the cortical surface (electrocorticogram).

Evoked Responses

An evoked response is the electrical activity produced in direct response to stimulation of one sensory system. A visual stimulus results in a *visual evoked response* (VER), an auditory stimulus provokes a *brainstem auditory evoked response* (BAER) and a sensory stimulus results in a *somatosensory evoked potential* (SSEP). These responses are of very low amplitude as compared to the background EEG activity. Hence, 100–1000 precisely timed stimuli are delivered and the responses recorded for a fixed time duration after each stimulus. These records are averaged using a computer. The random background activity tends to cancel out while the specific response grows larger with each repetition. The visual evoked response to an alternating black and white checker-board pattern is recorded over the occipital region. The normal latency is 100 milliseconds. A lesion of the optic nerve, even one which causes no abnormality on fundoscopy (retrobulbar neuritis), will

[1] The time interval between two adjacent lines on the EEG paper is 100 milliseconds at this standard speed.

prolong the latency. Hence patients with multiple sclerosis may show an abnormality of the VER even after their visual acuity has returned to normal. The auditory evoked response is useful in detecting and localising lesions within the brainstem. There are seven different waves; the first wave is generated from the auditory nerve, the third is generated in the medulla and the fifth in the midbrain. The somatosensory evoked response can be recorded following stimulation of the upper limbs or the lower limbs. A series of waves are recorded reflecting activity within the spinal cord, gracile and cuneate nuclei, thalamus and cerebral cortex. Lesions of the sensory path can be detected. Recently, using magnetic stimulators, specific parts of the motor cortex can be painlessly stimulated from the surface. A muscle contraction results and can be recorded. These *motor evoked responses* (MER) can define the integrity of central motor pathways. The latency period between the stimulus and the muscle contraction is called the *central conduction time.*

Techniques for evaluating the peripheral nervous system are discussed in section 9.9. These include the electromyogram, nerve conduction studies, muscle biopsy and nerve biopsy.

KEY CONCEPTS

Cerebrospinal fluid analysis

- Normal CSF is a clear colourless fluid with an opening pressure lower than 180 mm water; it has 0–3 cells/mm^3, a glucose content of 50–100 mg/dl (>60% of simultaneously obtained blood glucose) and a protein content of 20–45 mg/dl.
- CSF examination is useful for documenting intracranial pressure, and for the diagnosis of infection, inflammation, bleeding or malignancy originating from or extending to the subarachnoid space.
- Increased CSF protein indicates inflammation. Reduced CSF glucose indicates infection (bacterial/fungal) or sterile inflammation (SLE, Behcet syndrome).
- Bloody CSF may be due to a traumatic tap or due to a subarachnoid hemorrhage (*xanthochromia*)
- Increased polymorphonuclear cells suggest bacterial infection; increased mononuclear cells suggest viral infections, tuberculosis, partially treated bacterial meningitis.
- Important CSF tests: culture, Gram-stain, latex agglutination test (bacterial meningitis); Ziehl-Nielsen stain (tubercular meningitis), India ink stain (cryptococcal meningitis) and VDRL (syphilis) for infections; cytologic examination for suspected malignancies seeding meninges; oligoclonal bands, globulins, myelin basic protein for suspected demyelinating disease.

Computerised tomographic (CT) scan

- A CT scan provides rapid images of the cerebral cortex, ventricles and bony structures. It thereby identifies hemorrhage (increased density), edema, atrophy, mass lesions, demyelination, intracranial calcification (as in craniopharyngioma). It is advantageous relative to MRI in acutely ill patients.
- In a *contrast-enhanced CT* an intravenous injection of contrast identifies vascular malformations and areas where the blood-brain barrier is not intact.

Magnetic resonance imaging

- Generally, MRI provides better anatomic resolution than a CT scan; this is specially true for structures in the posterior fossa, white matter lesions, spinal cord diseases and syringomyelia.
- Injection of paramagnetic contrast (like gadolinium) further enhances resolution and is the method of choice for evaluating dural venous sinus thromboses.
- MRI is contraindicated in subjects with cardiac pacemakers, ferromagnetic aneurysm clips and metallic prostheses.

Carotid Doppler

- This is a technique which assesses the common carotids and extracranial internal carotids in the neck for stenoses, occlusions and ulcerated atherosclerotic plaques.
- Transcranial Doppler is used for evaluation of flow patterns within large intracranial arteries.
- Doppler evaluation is the non-invasive investigation of choice for evaluating patients with carotid TIAs.

Myelography

- X-ray of the spinal cord taken after injection of contrast into the subarachnoid space

- ➢ Myelography enables visualisation of intrinsic and extrinsic spinal tumours, herniated intervertebral discs, spondylotic bars and arachnoiditis.

Electroencephalography

- ➢ This is a method of recording electrical activity originating from the brain with scalp electrodes which is displayed as voltage (μV) versus time (Hz).
- ➢ Normal EEG shows β waves over the frontal cortex, α waves over the occipitoparietal cortex interspersed with θ waves.
- ➢ EEG is useful for the diagnosis of seizure disorders (bursts of sharp and slow wave 4–7 Hz in generalised tonic-clonic seizures; 3 Hz in petit mal; 1 Hz in Creutzfeldt-Jakob disease), sleep disorders, metabolic encephalo-pathies (slowing with δ activity).

Evoked potentials

- ➢ Cortical potentials recorded (using computer signal averaging) from specific neuroanatomic tracts activated by *visual* (*VER*), *auditory* (*BAER*), or *tactile (SSER)* stimuli.
- ➢ The latency, duration and amplitude reflect the integrity of the physiologic sensory pathways. *VER* is useful for the diagnosis of multiple sclerosis, identifying hysterical blindness, evaluating vision in comatose patients. *BAER* tests integrity of brainstem pathways while *SSER* is helpful in the localisation of diseases affecting plexuses or the spinal cord. *Motor evoked potentials* are elicited by transcranial stimulation and provide information about the integrity of central motor pathways.

9.4 Cerebrovascular diseases

STROKE: AN OVERVIEW

A stroke is a neurologic disorder, typically of abrupt onset, due to a disturbance of the blood supply to the central nervous system. If the disorder lasts for more than twenty-four hours, it is conventionally called a stroke. Transient symptoms of the same nature which last for less than 24 hours are referred to as *transient ischemic attacks* or TIAs.

Epidemiology The incidence of stroke is approximately 1 per 1000. Incidence rates increase sharply with age and are higher in men than in women. Stroke is a leading cause of morbidity and mortality worldwide. It is the third most frequent cause of death in developed countries. In these countries, however, total stroke mortality has shown a steady decline secondary to a reduced incidence of severe stroke. The most important factor for this decline in mortality appears to be the control of hypertension in individual patients and as a population mean. In India, we do not know if the incidence of stroke is declining. Also, in some Indian series, up to 30 per cent of strokes occur below the age of 40 years (*stroke in the young*). Other differences in stroke epidemiology include the greater frequency of stroke due to cardiac embolisation, and a higher frequency of idiopathic stroke.

Case fatality in severe stroke has not appreciably declined anywhere in the world. Hence, there is a new emphasis on treating stroke as a medical emergency.

Etiopathogenesis Strokes are broadly divided into two categories: ischemic and hemorrhagic.

Ischemic Stroke

Approximately 80 per cent of the time, the etiology of the stroke is too little blood reaching a portion of the central nervous system resulting in an ischemic stroke. The most frequent causes of such a stroke are in situ *thrombosis* occluding a vessel (50%) or an *embolus* (30%) carried by the blood stream to the site of occlusion. An embolus can arise from the heart (*cardiac embolus*), the aortic arch, arteries upstream to the site of occlusion (*artery to artery embolus*) or from the lungs and venous system after passing through a patent foramen ovale of a congenital right to left shunt (*paradoxic embolus*). The rarer causes of ischemic stroke may be thought of as attributable to diseases of 1) the *vessel wall* (inflammatory arteritis such as Takayasu's disease and systemic lupus erythematosus), and 2) *blood components* (hematologic disorders causing hypercoagulability). Various causes of ischemic stroke are listed in Table 9.8.

Atherosclerosis accounts for over 50 per cent of ischemic strokes. The major risk factors for ischemic stroke are similar to those for atherosclerosis and include age, (male) sex, hypertension, positive family history, diabetes mellitus, evidence of atherosclerosis (as indicated by coronary atherosclerosis, carotid bruit or previous stroke), obesity, smoking and the use of oral contraceptives; serum cholesterol appears to have a less significant effect on

increasing the risk for ischemic stroke (than in the risk of coronary artery disease). Marked narrowing of the carotid arteries and the presence of an ulcerated plaque indicate a higher risk for ischemic stroke.

The major risk factor for embolic stroke is **cardiac disease** (atrial fibrillation— idiopathic or due to rheumatic valve disease). Atrial fibrillation greatly increases the risk of embolic stroke to about 5 per cent year (in the absence of anticoagulation). The risk is maximal in elderly patients with hypertension, coronary or valve disease. The lowest risk is in young patients with 'lone' atrial fibrillation. Following a myocardial infarction, if there is a dyskinetic segment there is an increased risk of thrombus formation and subsequent embolisation. In dilated cardiomyopathies, upto 15 per cent of patients may develop an embolic stroke; this proportion doubles if atrial fibrillation is present. Upto 25 per cent of patients with rheumatic mitral stenosis develop systemic emboli, the risk being greatest in the presence of atrial fibrillation. Prosthetic heart valves carry a high risk of systemic embolism, with mechanical valves having a higher risk than bioprosthetic ones. The risk is roughly equal in anticoagulated patients with mechanical valves and non-anticoagulated patients with bioprosthetic valves: 2 per cent per year for aortic and 4 per cent per year for mitral prostheses.

Hemorrhagic Stroke

About 20 per cent of all strokes are hemorrhagic. The types of hemorrhagic stroke are:

1. **Intraparenchymal** (66%). Such hemorrhages may be secondary to hypertension or may be due to other causes. Hypertensive hemorrhages affect the following structures in order of

Table 9.8 Causes of ischemic stroke

1. Atherosclerosis
2. Cardiac emboli
   - mural thrombus following myocardial infarction/cardiomyopathy
   - left atrial thrombus in mitral valve disease/atrial fibrillation
   - valve thrombus in prosthetic valve thrombosis, bacterial endocarditis
   - cardiac myxomas
3. Vasculitis
   - secondary to chronic meningitis (tuberculosis, syphilis, fungal)
   - immunoinflammatory disease (polyarteritis nodosa, SLE, giant cell arteritis, Behcet's disease, primary cerebral vasculitis)
4. Hematologic disorders
   - sickle cell anemia
   - hyperviscosity syndromes (polycythemia, multiple myeloma, macroglobulinemia)
   - hypercoagulable states (pregnancy, puerperium, carcinoma, thrombotic thrombocytopenic purpura, antiphospholipid antibodies, protein C or S deficiency)
5. Miscellaneous
   - homocystinuria
   - fibromuscular dysplasia
   - arterial dissection
   - vasospasm following subarachnoid hemorrhage
   - complicated migraine
   - air and fat embolism
   - Moya-Moya disease

frequency: basal ganglia (putaminocaudate–50%), thalamic (15%), brainstem (pontine–15%) and cerebellar (20%). Bleeding in hypertensive hemorrhage arises from rupture of microaneurysms (*Charcot-Bouchard aneurysms*) located in small (100 μ) penetrating arteries. Hypertension causes fibrinoid necrosis of the vessel wall. Non-hypertensive hemorrhage is typically lobar, involving the subcortical white matter. Common causes include vascular malformations, an entity called amyloid angiopathy[1] and the various bleeding diathesis.

2. **Intraventricular hemorrhage**, which may be primary or secondary to an intraparenchymal bleed.

3. **Subarachnoid hemorrhage** (about 33%): The commonest cause of subarachnoid hemorrhage is rupture of a saccular or *berry* aneurysm.

4. **Traumatic intracranial hemorrhage** is a distinct entity discussed in the section on head injuries. Common locations include epidural, subdural, intraparenchymal and, rarely, the subarachnoid space.

Clinical syndromes If there is a sudden onset neurological deficit (stroke) the two aspects of clinical evaluation are determining the type of stroke, and the site of the stroke. For the former the setting, temporal profile of onset and progression and level of sensorium are useful. For instance, a patient with hypertension presenting with an apoplectic onset loss of consciousness is likely to have a hemorrhagic stroke. To determine the site, neurological examination and correlation with knowledge of brain and vascular anatomy are required. This neurological examination should be tailored to the patient's sensorium and aimed at quickly determining the structures involved: pupils, oculomotor nerve, seventh nerve, gag reflex, twelfth nerve, motor, gross sensory and deep tendon reflexes in all four limbs, plantar reflexes, and bladder involvement. General physical examination should include examination of the head and neck area (carotids, ocular vessels, subclavian and vertebral arteries) for asymmetry in pulses and bruits. Peripheral pulses are also examined (Takayasu's arteritis, coarctation, aortic dissection). Cardiac auscultation and examination of the lungs are important to trace the cardiac source of embolism and to exclude aspiration pneumonitis secondary to the stroke. The importance of quickly evaluating all organ systems cannot be overemphasised as patients with a wide variety of disorders (e.g. renal failure, SLE, leukemia) may present with a stroke syndrome. It is important to remember that stroke is only a syndrome which may be due to a variety of causes. Variants of stroke such as stroke following meningitis should not be forgotten. Other important considerations in the differential diagnosis are subdural hematoma, brain tumour, brain abscess, tuberculoma, cysticercosis, a postictal paralysis and complicated migraine.

Management of stroke: general principles 30 per cent of patients who suffer a stroke die of their stroke. Despite this, a developing stroke often does not evoke the same degree of urgency in response that a suspected myocardial infarction does. To counteract this prevailing tide of nihilism, the American Heart Association recently included emergent stroke care as part of its special resuscitation situations, calling it a 'brain attack' and mounting a patient education campaign.

Acute care: Basic tests in the emergency room include an ECG to rule out cardiac arrhythmia or an infarct[2] and laboratory tests (hemoglobin,

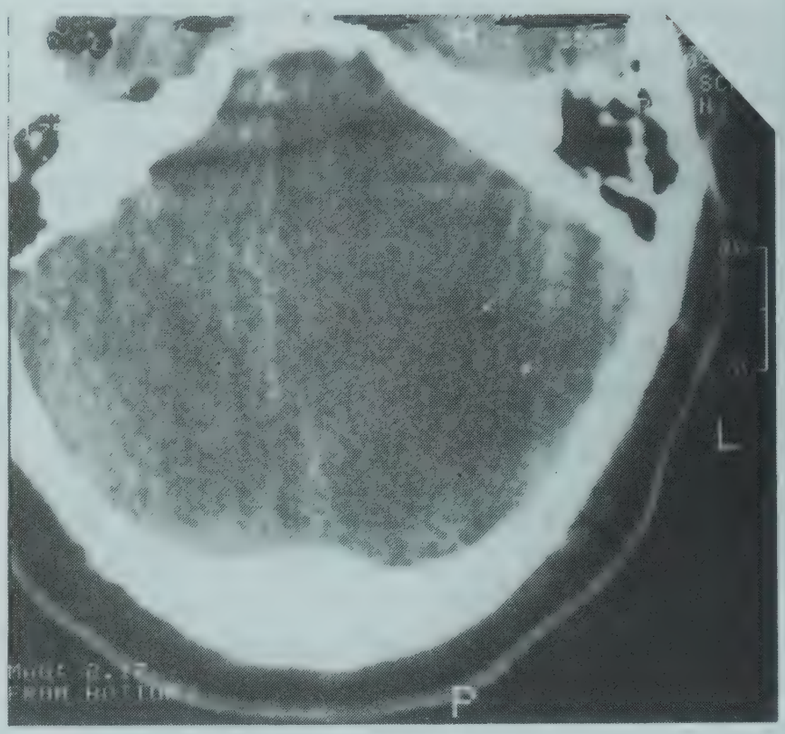
[1] Amyloid angiopathy is a condition seen in the elderly wherein amyloid deposits are found within the media and adventitia of the small- and medium-sized arteries. Imaging studies show periventricular lucencies and white matter atrophy. Multiple small subclinical hemorrhages and infarcts may occur and the clinical presentation may be as a dementia or a large hemorrhage.

[2] Some strokes can cause secondary ECG changes including ST elevation, T inversion, QRS widening and QT prolongation; a cardiologist's opinion should be sought to differentiate primary cardiac and secondary ECG abnormalities.

white cell counts, blood smear, a random blood glucose and serum sodium and potassium). Patients with acute stroke should be admitted for monitoring.

A tentative diagnosis should be clinically established before obtaining a computerised tomographic (CT) scan of the head (Figs 9.11, 9.12, 9.13). The purpose of the CT scan is to differentiate between hemorrhage and ischemic stroke and to exclude a structural lesion (such as a tumour). A normal CT scan in the presence of a clinical stroke suggests that the stroke is ischemic. The true extent of infarction in an ischemic stroke is best seen after 48 hours.[1] Because of this and in the interests of cost control (avoiding two CT scans), the CT scan could be deferred in conscious patients for 48–72 hours but these patients should be carefully monitored and a CT scan done if there is any

1 Early signs of infarction may be subtle. The normal distinction between grey and white matter may become blurred. In middle cerebral artery strokes, due to stasis, a small segment of the artery may become visible (dense artery sign).



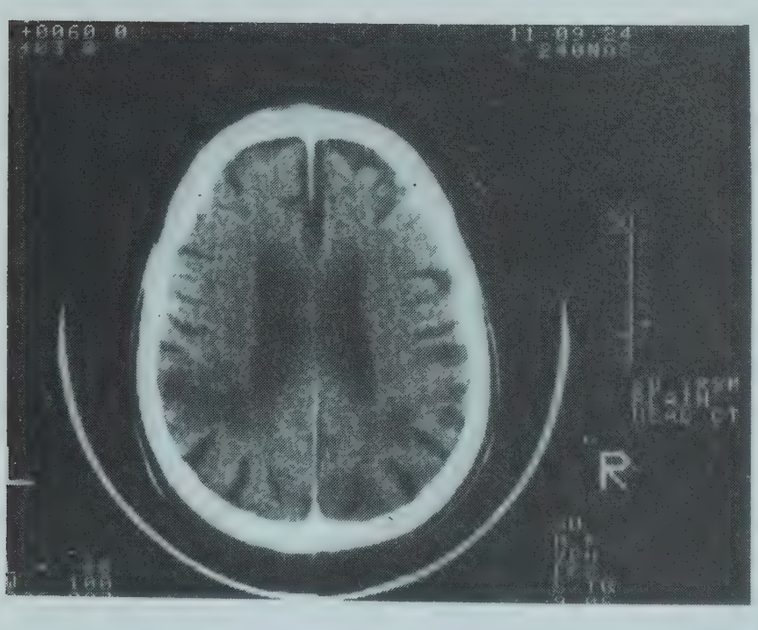


Fig 9.11 The CT scan shows a week old infarct in the left parietal area (MCA [middle cerebral artery] territory). Most of the MCA territory is spared, suggesting an occlusion of only one branch.

Fig 9.12 CECT appearance in a patient with a large clot at the 'top of the basilar artery'. There is a large right PCA infarct and a cerebellar infarct (SCA). Both the PCA and the SCA arise from the basilar artery. This patient died.

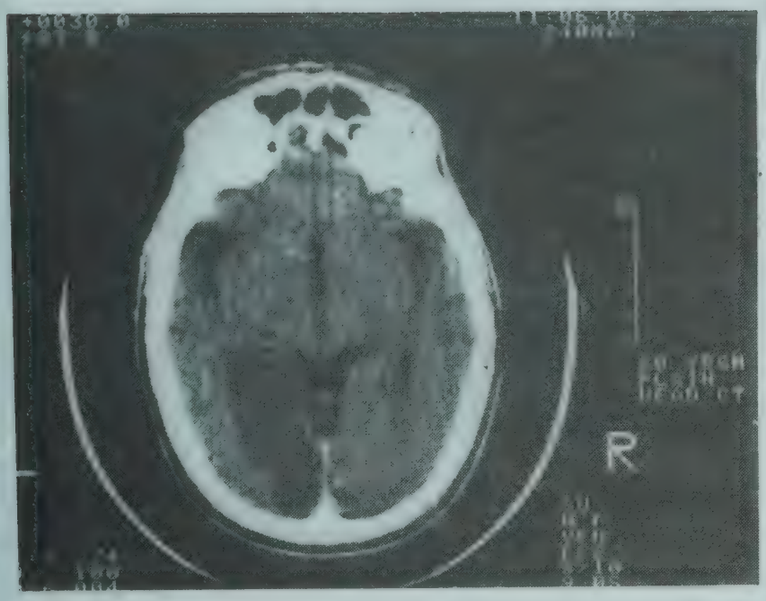


Fig 9.13 The CT scan shows a recent infarct on the left side—the medial temporooccipital lobe (PCA territory). The patient had right homonymous hemianopia.

progression of signs or deterioration in consciousness. Clinical differentiation between infarction and hemorrhage has proved quite unreliable. Even using specialised scales developed in the pre-CT era, clinical diagnosis is right in differentiating the two conditions only a little more than 50 per cent of the time. Magnetic resonance imaging is not indicated in acute stroke. It is less freely available and more expensive. In an acutely ill patient, motion artifacts occur and monitoring is difficult. Finally, MRI may not be reliable in detecting acute hemorrhage. The potential advantages of MRI in a stable patient are earlier detection of ischemic infarction and better visualisation of brainstem strokes.

Subsequent investigations (in the ward), may include a fasting blood glucose and lipid profile (cholesterol, triglycerides); ESR, RPR, ANA and urine examination to look for vasculitides, chest X-ray if the patient is unconscious (to look for pneumonia due to aspiration) and arterial blood gas analysis (to assess ventilation if the patient is comatose with tachypnea, irregular respiration or aspiration); platelet count, prothrombin time (PT), and partial thromboplastin time (PTT) as a screening test for bleeding diatheses and hypercoagulable states. EEG may be useful in ruling out ongoing seizures. Renal and liver function tests may be performed to obtain a baseline if prolonged altered sensorium is likely.

A lumbar puncture is indicated only if subarachnoid hemorrhage is suspected but not confirmed with a CT scan, or if there is a reasonable suspicion of a meningitic process simulating or resulting in stroke.

Assessment of the aorta, the carotids and the vertebral arteries and cardiac assessment in cases of suspected embolic stroke are discussed in detail in the section on ischemic stroke.

The principles of therapy in all stroke patients include supportive therapy to maintain the patient's health and comfort, prevention of infarct extension, avoiding neurological complications, and preventing immediate or delayed recurrence.

Supportive care: Constipation is avoided by routine use of a bulk laxative in all non-ambulatory patients. Paracetamol is given to treat fever or pain and is preferable to a platelet-inhibiting agent such as aspirin. Bedrest for 24 hours is usually advised but patients may be allowed to use the bathroom if they are walking easily.

In patients with altered sensorium or bulbar dysfunction, the priorities include the prevention of secondary complications:

1. *Maintain nutrition and metabolic balance*: The unconscious stroke patient is initially maintained on 'nil oral' orders and isotonic fluids. If this condition persists for more than 24 hours, the patient requires hyperalimentation and not just fluids and glucose. Care should be taken to maintain electrolyte balance and caloric intake. An intake-output chart is maintained and reviewed by the physician at least once every 12 hours changing orders as needed; daily

electrolyte monitoring is prudent– patients with acute cranial lesions often develop a syndrome of inappropriate antidiuretic hormone secretion resulting in hyponatremia. Avoid hyperglycemia or hypoglycemia as both may increase the severity of the stroke. Nasogastric tube (Ryle's tube) feeds are usually possible in 24–48 hours. Care is taken to prevent gastric distension and aspiration. Feeds should be small and frequent (2 hourly) with nasogastric tube aspiration prior to the next feed to confirm that the stomach has emptied. The advantage of initiating early nasogastric tube feeding is that it is easier to avoid electrolyte imbalances and provide sufficient calories; the disadvantage is that the chronic presence of a foreign object in the pharynx further weakens the gag reflex. Once swallowing returns (and sensorium is adequate), oral feeds should be resumed starting with semisolids. If the integrity of the swallowing reflex is in doubt, a barium swallow is performed prior to initiating feeds.

2. *Prevent falls, injury*: While the patient is comatose, bed rails should be used. Later the patient should be advised to stand or move only with adequate supervision until she has adapted to her deficit and postural hypotension has been excluded. Restraints should be used sparingly.

3. *Prevent infection* (aspiration pneumonia, UTI): The patient should be nursed on the side (semi-prone) and the head end of the bed elevated by 30 degrees. It may be necessary to protect the airway with a cuffed nasotracheal, endotracheal or tracheostomy tube in some patients.

To prevent urinary tract infection, it is better to use a condom catheter for men rather than an indwelling catheter. The urine bag should be changed once in 2–3 days. During nursing procedures one should never raise the bag above the level of the catheter as this results in reflux of urine from the bag to the catheter increasing the risk of infection. In both sexes local hygiene is important. In conscious patients, catheters should be avoided as far as possible; if the patient is incontinent, diapers are preferable if these are available and can be changed frequently.

4. *Prevent pulmonary thromboembolism*: Heparin 5000u injected subcutaneously q 12 hours, passive physiotherapy, compression stockings and early ambulation are advised with the aim of preventing deep venous thromboses.

Prevention of extension, complications and recurrence are discussed specifically for each type of stroke.

Rehabilitation and long-term care: Despite the best care, a third of patients who suffer an acute stroke will be left with significant disabilities. The physical disability may be a speech defect (in understanding or expression), inability to use the dominant upper limb, difficulty in walking, subtle difficulties in carrying out complex tasks or, in extreme cases, the patient may remain bedridden requiring long-term supportive and nursing care. As a result, poststroke depression is common. Recovery from stroke is fastest in the first few weeks (resolution of edema and recovery of function in some neurons) but may continue for upto six months; the patient adapts and achieves 'old ends' by 'new means'.

Well-organised stroke rehabilitation services make a significant difference in the patient's independence. The initial emphasis is on passive physiotherapy and prevention of contractures. Later the patient may need antidepressants or analgesics. A disused limb may develop painful arthritis, particularly at the shoulder joint; this can be prevented by regular physiotherapy. Speech therapy can be beneficial. Occupational therapy is a branch where the patient is taught to be independent as far as possible by the innovative use of residual functions and special devices (often simple ones like using a spoon with a larger handle which is easier to grip).

DESCRIPTION OF INDIVIDUAL STROKE SYNDROMES

Ischemic Strokes

The causes of ischemic stroke have been discussed earlier. At the time when a patient presents it may not be clear if the neurologic deficit will continue to progress *(stroke-in-evolution)* or whether no further deterioration will occur (*completed stroke*). The clinical presentation of ischemic stroke enables one to predict with reasonable certainty which cerebral artery is occluded.

Internal carotid artery occlusion

Stenosis of the internal carotid artery may be classified as insignificant (<50%), mild (50–70%), moderate (70–90%) or severe (>90%). With any degree of stenosis, the clinical symptomatology depends on the adequacy of collateral circulation through the circle of Willis. At one end, the patient may be completely asymptomatic, despite occlusion of one artery. In this case, a fresh occlusion of the opposite artery can lead to a devastating bilateral stroke. Occlusion of the internal carotid artery usually results in dense contralateral hemiplegia. There may be monocular blindness due to involvement of the ophthalmic or central retinal arteries.

The middle cerebral artery

The middle cerebral artery is the commonest site for embolic occlusion, but overall it is more likely to be involved in a thrombotic stroke. The middle cerebral aretery in its proximal portion gives rise to penetrating end arteries which supply the basal ganglia and the internal capsule. It then divides into a superior division which supplies the primary motor and sensory cortices and an inferior division which supplies the association areas of the parietal and lateral temporal cortex. The resulting symptoms depend on whether the dominant or non-dominant hemisphere is affected and on whether some or all of these branches are involved. Involvement of the dominant hemisphere leads to language dysfunction (motor, sensory or global aphasia) and involvement of the non-dominant hemisphere lead to visuospatial dysfunction. (In right-handed patients the left cerebral hemisphere is almost always dominant. In left-handed patients, the right cerebral hemisphere is dominant 50 per cent of the time.) Other symptoms include contralateral hemiparesis, sensory loss and visual field defects (hemianopsia). Upper limb involvement is more severe than lower limb involvement,[1] since the upper limbs are represented in the lateral portion of the motor strip which is supplied exclusively by the middle cerebral hemisphere. The lower limb is represented in the medial portion of the motor cortex, an area which may have substantial collateral supply from the anterior cerebral artery. A right-sided stroke may present with neglect of the opposite side so that the patient is unaware of external stimuli or even his own body parts on the left. An old stroke in the middle cerebral distribution, particularly one that occurred in childhood, may show dystonia and diminution in size of the affected limb (parietal hand syndrome).

The anterior cerebral artery

The anterior cerebral artery supplies the medial frontal lobe. Infarction of the anterior cerebral artery results in a syndrome of abulia or hypobulia (slowing of verbal and motor responses) and a hemiparesis wherein the lower limb is weaker than the upper limb. Since both anterior cerebral arteries often receive their blood supply from one internal carotid, infarction may be bilateral. In this case profound abulia is associated with paraplegia and bladder dysfunction (urinary retention). Frontal lobe release reflexes (grasp, following) are prominent.

[1] Partial syndromes such as *faciobrachial paresis* may be seen.

The posterior cerebral artery

Involvement of the posterior cerebral artery can cause isolated contralateral homonymous hemianopsia. There may be preservation of a central island of macular vision because fibres from this area go to both occipital poles. Other syndromes include cortical blindness (due to involvement of both occipital lobes), Anton syndrome (the patient is blind but denies it and describes imaginary objects), alexia and colour anomia. Less commonly there may be memory defects if the posterior cerebral artery supplies both hippocampi. At its origin, the posterior cerebral artery gives off a number of branches to the thalamus, subthalamus and upper midbrain. Occlusion of these can result in hemiparesis (cerebral peduncle), ataxia and tremor (red nucleus), oculomotor paresis (third nerve nucleus), hemiballismus (subthalamic nucleus of Luys). Thalamic infarction can cause contralateral sensory impairment followed a few weeks later by agonising pain in the anesthetic areas (thalamic pain syndrome of Dejerine).

The vertebral arteries

The vertebral arteries give off two cerebellar arteries, supply small arteries to the medial part of the medulla and then join to form the basilar artery. The two cerebellar arteries are called the posterior inferior cerebellar artery (PICA) and the anterior inferior cerebellar artery (AICA). Occlusion of the vertebral or the PICA results in a characteristic syndrome called the *lateral medullary syndrome*. As its name implies, structures in the lateral part of the medulla are affected. The clinical features are described in Table 9.9. Note that there is no hemiparesis or hypoglossal paresis since these structures are in the medial medulla. Hiccups are often persistent and distressing in this syndrome.

The basilar artery

The basilar artery supplies the superior cerebellum, the entire pons and most of the midbrain. Infarction of the pontine tegmentum can result in a 'locked-in' syndrome. An embolus to the basilar artery is often impacted at its most distal portion resulting in a '*top of the basilar*' syndrome as described in the section on coma.

From a practical point of view, it is more important to identify a stroke as a vertebrobasilar or brainstem stroke (as distinct from an anterior circulation stroke) than to precisely localise the brainstem structures involved. Clues to a brainstem etiology include:

1. 'crossed' hemiparesis or hemisensory loss wherein the face is affected on one side and the opposite limbs are involved;

Table 9.9 Clinical features of the lateral medullary syndrome

Structure	*Clinical features*
Inferior cerebellar peduncle	Cerebellar ataxia (patient falls towards side of lesion)
Descending spinal tract of trigeminal nerve	Pain and numbness over ipsilateral half of face
Vestibular nucleus	Vertigo, nausea, nystagmus
Glossopharyngeal and vagus nerves	Dysphagia, hoarseness
Descending sympathetic tract	Horner syndrome
Nucleus tractus solitarius	Loss of taste
Cuneate and gracile nuclei	Impaired vibration and joint position sense in ipsilateral limbs
Spinothalamic tract (afferent fibres cross at the spinal level)	Contralateral loss of pain and temperature sensation

2. diplopia, nystagmus and vertigo are present;
3. a lower motor neuron type involvement of the cranial nerves such as the hypoglossal nerve.

Dysarthria may be seen with brainstem or deep hemispheric lesions but dysphasia is only seen with cortical lesions.

Lacunar strokes

Small, subcortical infarcts ranging in size from 0.3 to 2 cm are called lacunar infarcts. They result from occlusion of an end artery arising from the proximal middle cerebral artery, vertebral or basilar arteries. A variety of characteristic clinical syndromes are described as 'lacunar syndromes' although they can also occur with partial occlusion of larger arteries. Ten per cent of all strokes are lacunar. Common lacunar syndromes are described in Table 9.10.

Table 9.10 Types of lacunar syndrome

Structure	*Site of lesion*
Pure motor	Posterior limb of internal capsule, basis pontis
Pure sensory	Thalamus and parietal white matter*
Clumsy hand– dysarthria	Basis pontis
Dense isolated sensori-motor deficit	Posterior limb of internal capsule,

* Cortical sensory impairment presents with impaired stereognosis and two-point discrimination while capsular or thalamic stroke results in impairment of primary sensory modalities.

Pathophysiology The brain autoregulates its blood flow, that is it attempts to maintain a constant blood flow in the face of disturbances to the steady-state such as a drop in the cerebral perfusion pressure. The normal range of cerebral perfusion pressure is 50–150 mmHg. The different stages in the brain's autoregulatory response are described in the box.

Stages 2 and 3 are potentially reversible and constitute the *ischemic penumbra* around the infarcted area. Newer imaging techniques such as positron emission tomography (PET), single photon emission computerised tomography (SPECT) and functional magnetic resonance imaging can differentiate between these stages (perfusion and metabolic scans).

Pathology An infarcted brain is initially pale. Within hours to days, the area becomes congested with dilated blood vessels and minute petechial hemorrhages. If the etiology is embolic, the embolus may migrate, lyse or disperse and recirculation into the ischemic area causes bleeding from the necrosed vessels; this results in hemorrhagic infarction.

Management As defined in the principles section, the management of ischemic stroke involves supportive care (discussed earlier), prevention of extension, prevention of complications, prevention of recurrence and rehabilitation (discussed earlier).

Prevention of extension of ischemic stroke:

1. Optimising blood pressure: In the immediate poststroke period an elevated blood pressure can result from the stress of a stroke, a full bladder, pain, preexisting hypertension or raised intracranial tension. These factors should be corrected if possible. Drug therapy for stroke should be cautious as rapid lowering of blood pressure particularly in a patient with preexisting hypertension can lead to extension of the infarct. If the pressure is >130 mmHg (mean) or 200 mmHg (systolic) oral therapy with captopril or a calcium-blocking agent should be initiated. Intravenous drugs are rarely indicated. Sublingual medication (nifedipine) can cause rapid lowering of blood pressure and should be avoided.
2. Cytoprotection: Cytoprotective (neuroprotective) drugs are agents believed to protect brain tissue from ischemic damage because they act on specific steps along the metabolic pathway which mediates ischemic necrosis. Various cytoprotective agents have been used including steroids, barbiturates and naloxone but none of these has been found useful in controlled clinical trials. Oral nimodipine may be effective in reducing the severity of ischemic stroke but intravenous nimodipine is contraindicated as it may lead to

Stage 1	Vasodilation	Blood volume increases but rate of flow remains low so that the oxygen extraction ratio is lowered (called '*luxury*' perfusion)
Stage 2	Tissue ischemia (despite vasodilation, flow less than 40 ml/100 g/min)	Gradually rising extraction ratios for oxygen and glucose
Stage 3	Ischemic injury (flow 10–20 ml/100 g/min)	Cells stop functioning and glucose utilisation and oxygen extraction fall (*hibernating tissue*)
Stage 4	Ischemic death (flow less than 10 ml/100 g/min)	Ionic pumps fail resulting in intracellular calcium entry; activation of proteases and cell swelling results in *necrotic cell death*

hypotension. Newer agents, such as glutamate antagonists and free radical scavengers (21 amino steroids, GM1 gangliosides) are being evaluated.

3. Hemodilution: The theoretical basis of using hemodilution for treating stroke was that lowering the blood viscosity by administration of fluids might improve cerebral blood flow. In patients with polycythemia who develop a stroke, gradual lowering of the hematocrit (if it is above their usual basal level prior to the stroke) is accepted but not proven therapy. In other patients with a hematocrit in the normal range, trials have shown no benefit. There are two kinds of hemodilution which have been attempted: isovolemic (giving hypotonic solutions like 5% dextrose to lower hematocrit by 15%), and hypervolemic (giving dextran, pentastarch); the latter may actually increase mortality.

4. Hemorrheologic agents such as pentoxifylline yield no benefit.

5. Acute thrombolysis: Intravenous heparin or heparinoids are given for progressing basilar artery stroke, particularly if the etiology is thought to be embolic. In carotid obstruction, trials of intravenous (systemic) and intraarterial (local) administration of tissue plasminogen activator and streptokinase have been undertaken. Preliminary results suggest a benefit if the drug is administered within 4 hours of onset of stroke. However, the risk of hemorrhagic transformation rises significantly.

6. Acute surgical procedures such as carotid endarterectomy, embolectomy, and carotid angioplasty have been attempted. Determination of the site of obstruction is easy but periprocedural worsening of infarction is frequent enough to make the risk-benefit ratio adverse at the present time.

7. Hyperglycemia and hypoglycemia should be avoided. Routine supplemental oxygen is not useful but patients with documented hypoxia merit oxygen supplementation and appropriate respiratory support.

Prevention of complications of ischemic stroke: Acute neurological complications are cerebral edema and raised intracranial pressure (which can lead to herniation, brainstem compression and death), seizures, and hemorrhagic transformation.

1. Cerebral edema occurs in about 15 per cent of stroke patients, particularly if the area of infarction is large. Peak swelling occurs 3 to 5 days after the stroke. In cerebellar infarction there may be obstruction of the fourth ventricle resulting in acute hydrocephalus within 24 hours. Treatment modalities of proven efficacy are hyperventilation (a 5 mmHg reduction in PCO_2 immediately lowers intracranial pressure by 25 per cent). To maintain this effect, hyperosmolar agents (drugs which increase serum osmolality, thereby drawing water from the brain cells into the blood stream)

are used. Intravenous mannitol (0.3 g/kg given over 20 minutes) may be given every 6 hours. Oral glycerol may be effective. Intravenous furosemide is of doubtful efficacy. Corticosteroids are not useful and may cause gastrointestinal hemorrhage.[1] These agents should be used only if the risk of herniation appears high (large infarct, deterioration in sensorium). Repeated prolonged use is probably counterproductive. In large cerebellar infarctions surgical debulking may be life-saving. Surgical debulking is usually not indicated in large hemispheric infarcts since the patient is left with very severe deficits.

2. Seizures occur in approximately 5 per cent of patients in the first 24 hours following a stroke. They are easily controlled with anticonvulsants– a loading dose should be given if phenytoin is used. Anticonvulsants should be continued for 6 months to prevent seizure recurrence but prophylactic anticonvulsants are not indicated.

3. Hemorrhagic transformation occurs in 5 per cent of strokes. Low dose heparin does not appear to significantly increase this risk but aspirin and anticoagulants should be used cautiously if the area of infarction is large.

Prevention of recurrence: 1. Improvement of stroke risk profile: The risk factors for ischemic stroke have been described earlier. These should be modified as much as possible. This includes cessation of smoking, and control of hypertension, hyperlipidemia and hyperglycemia. In patients who are not known to be hypertensive, transient elevation of blood pressure following stroke is not a good predictor of the need for long term antihypertensive therapy. However, if the ECG shows left ventricular hypertrophy, the fundus shows changes of longstanding hypertension or the high blood pressure persists at the end of 4 weeks, the patient requires definitive treatment for high blood pressure. Similarly, transient hyperglycemia in the immediate post-stroke period should not result in a diagnosis of diabetes. Fasting and postprandial blood sugar should be repeated after the patient's condition has stabilised.

2. Preventing recurrence of cardioembolic stroke: In all patients with stroke, routine ECG and chest X-rays are usually obtained. The former would detect recent or old myocardial infarction and cardiac arrhythmias such as atrial fibrillation (if present at the time of recording). The latter can give clues to the presence of congestive heart failure, aortic pathology (dilatation, calcification) or pulmonary pathology (paradoxical embolus). Other cardiovascular studies are ordered selectively based on clinical evaluation by a cardiologist. These may include Holter monitoring to detect intermittent arrhythmias and transthoracic echocardiography to detect wall motion abnormalities, thrombi, valve dysfunction and right to left shunts. Finally, transesophageal echocardiography is useful in detecting thrombi in the left atrium and aortic abnormalities. Prevention of recurrence may involve treatment of arrhythmias, or anticoagulation. Anticoagulation is indicated for patients with atrial fibrillation, dilated cardiomyopathy as well as postmyocardial infarction patients with mural thrombi.

3. Preventing recurrence of arterial stroke: The carotid and vertebral vessels should be imaged in any patient who suffers a stroke. The most common technique used is a duplex ultrasound of both carotids and vertebral arteries. This test combines B-mode imaging of the vessel wall with Doppler imaging of the flow within. Other techniques include MRI which is not yet as reliable as a duplex ultrasound for the neck vessels, but is an excellent alternative to conventional angiography for evaluating intracranial vasculature. Transcranial ultrasound has the advantage that it may be done repeatedly to look at changes in the intracranial vascular diameter over a period of time. Options for secondary prophylaxis include antiplatelet drugs (aspirin, ticlopidine) and carotid

[1] Corticosteroids are widely used in acute stroke to prevent rebound after the effect of the mannitol wears off; the scientific basis for this practice is unclear.

endarterectomy. The choice of the option is guided by the general health of the patient, the amount of brain tissue at risk, whether or not the patient is having TIAs and finally, the degree of stenosis.[1]

Transient Ischemic Attack (TIA)

This is a brief episode of focal loss of brain function, believed to be due to ischemia, which can usually be localised to a part of the brain supplied by one vascular system (left or right carotid or vertebrobasilar system) and for which no other cause can be found. By convention, the episodes last less than 24 hours. Most TIAs, however, have a sudden onset and last for only 2–15 minutes. Longer episodes are often associated with CT abnormalities and may represent infarcts. By definition, a TIA leaves no persistent deficit. Often there are multiple attacks (1 per year to 30 per day). Manifestations of a carotid TIA include transient monocular blindness (*amaurosis fugax*), hemisensory symptoms (numbness or paresthesia that may involve only one limb), motor dysfunction (dysarthria, weakness or clumsiness), aphasia and rarely, homonymous hemianopsia. The *amaurosis fugax* occurs on the same side as the arterial obstruction while the other symptoms are referred to the opposite side.

Symptoms suggestive of vertebrobasilar TIA include bilateral visual loss, ataxia, quadriparesis and perioral numbness. The commonest symptoms consist of vertigo, diplopia, dysphagia and dysarthria. Occurrence of any one of these four is not considered sufficient to diagnose a TIA; only when any two of these features occur together is a TIA diagnosed.

The management of TIAs consists in evaluating the 'culprit' vasculature for degree of stenosis and initiating of antithrombotic medication, or recommending revascularisation with a view to reducing the frequency of TIA as well as the risk of stroke. The current approach is to recommend carotid endarterectomy for patients with severe stenosis of 70–99 per cent with the proviso that the expected combined morbidity and mortality risk of the presurgical angiogram and risk of surgery should be below 3 per cent. Thus surgery should be performed only in centres backed by experience and patients with severe coronary artery disease would not be suitable candidates. In patients with carotid stenosis of under 50 per cent and in patients with vertebrobasilar stenosis no surgical procedure is currently advised. In a patient with 50–70 per cent carotid stenosis the role of surgery is unclear. All patients not suitable for surgery should be prescribed either aspirin or ticlopidine. Aspirin is initiated at a dose of half tablet daily (150 mg) but doses of up to 2 tablets per day may be required as higher doses appear to be more effective in certain patients. Ticlopidine (250 mg twice daily) may be tried if aspirin is not effective. The risk of hemorrhage is similar to that of aspirin. Other side effects of ticlopidine include rash, diarrhea and neutropenia. Ticlopidine is also more expensive.

Asymptomatic Carotid Stenosis

Carotid stenosis may be detected in an asymptomatic subject if a carotid bruit is heard on routine examination, or a carotid ultrasound is done as part of preoperative evaluation (prior to cardiac surgery). If a bruit is heard, carotid ultrasound is indicated. If carotid stenosis is identified, control of modifiable risk factors and aspirin ($^1/_2$ to 1 tablet daily) should be initiated, unless there are contraindications to aspirin therapy. If the degree of carotid stenosis is greater than 60 per cent, carotid endarterectomy has been shown to reduce the risk of stroke by 50 per cent over a five-year period. However, opting for this procedure carries a risk for stroke during the preoperative angiogram or during

[1] Two previously popular prophylactic options, which are no longer used, are 1) dipyridamole, an antiplatelet agent which is not useful for preventing stroke and 2) extracranial-intracranial bypass, a surgical procedure anastomosing the superficial temporal artery, a branch of the external carotid to the middle cerebral. This surgery was performed to circumvent intracranial stenosis of the internal carotid but a large study showed no benefit.

surgery. If the patient is in poor health, or is averse to taking an immediate risk or if the treating centre has a procedural morbidity greater than 3 per cent, carotid endarterectomy should not be done.

Cerebral Venous Thrombosis

Thrombosis of the cerebral venous system may involve the dural sinuses alone or the dural sinuses in conjunction with the cortical veins.

Etiology The causes of cerebral venous thrombosis can be divided into two groups: 1) there may be a hypercoagulable state as seen in the postpartum state; or 2) infection in a structure adjacent to a dural venous sinus (such as the middle ear) can result in aseptic thrombosis of the adjacent vein. If the thrombus becomes infected, the condition is called septic cortical sinus thrombophlebitis (for example, cavernous sinus thrombo-phlebitis).

Clinical features The clinical presentations can be varied. In descending order of frequency, they are: 1) progressive onset of intracranial hypertension over 2–3 days; 2) sudden onset of a focal deficit which mimics an arterial stroke but may not conform to arterial territories and is more likely to be associated with seizures; 3) a gradually evolving focal deficit with intracranial hypertension (resembling a mass lesion); and 4) sudden onset of severe headache.

Investigations Cerebral angiography is the gold standard for diagnosing this condition. The thrombosed veins are not seen during the venous phase of the study. A digital subtraction angiogram is preferred when available. The CT scan may show areas of cerebral edema and hemorrhagic infarction. The thrombosed vein may be visible without contrast (*cord sign*) but will not be visible after the contrast injection. If the superior sagittal sinus is thrombosed, an empty triangular shape is seen at the junction of this sinus with the sigmoid sinus (*delta sign*). On an MRI scan, the thrombus is hypointense initially and later hyperintense on T_2-weighted images. If available, magnetic resonance angiography can show the entire venous system non-invasively and becomes the diagnostic test of choice.

Management Intravenous heparin as a continuous infusion of 10–50 u/kg/hr (maintaining PTT at twice control levels) or as intermittent doses of 5000 u i.v. 6 hourly, aids clot lysis and prevents further extension or thrombosis. Anticonvulsants are administered, the usual agent being diphenylhydantoin (dose of 200–300 mg/day, following a loading dose). Mannitol is given to lower raised intracranial tension. Standard supportive care for the comatose patient is initiated. If the patient is peripartum, care of the breast is important. One should aim at enabling long term breast feeding by periodic pumping of breast milk rather than administering drugs to suppress lactation. Antibiotics may be indicated if a focus of infection is present.

Intracerebral Hemorrhage

Most intracerebral hemorrhages are secondary to hypertension. Other causes have been discussed earlier.

Pathophysiology Intracerebral hemorrhage usually arises from penetrating branches of major arteries. These medium-sized vessels respond to systemic hypertension with *lipohyalinotic*[1] changes in the media. The weakened vessel wall gives rise to small microaneurysms which may be the site of hemorrhage. Because the hemorrhage is arising from an artery and the pressure differential between the lumen and the surrounding parenchyma is high, the hemorrhage may reach full size in just a few minutes. Some

[1] Lipohyalinosis is a microscopic appearance in which the muscle of the arterial media is replaced by eosinophilic hyalin material thought to be a protein exudate; there may be associated fibrinoid necrosis.

hemorrhages, however, continue to grow slowly thereafter for upto an hour, and in patients on anticoagulants, for upto a day. The hemorrhage may extend into the ventricle or the subarachnoid space. In an intracerebral hemorrhage the neurologic deficit is due to displacement, compression and edema in adjacent brain tissue. As these resolve, there may be considerable functional recovery.

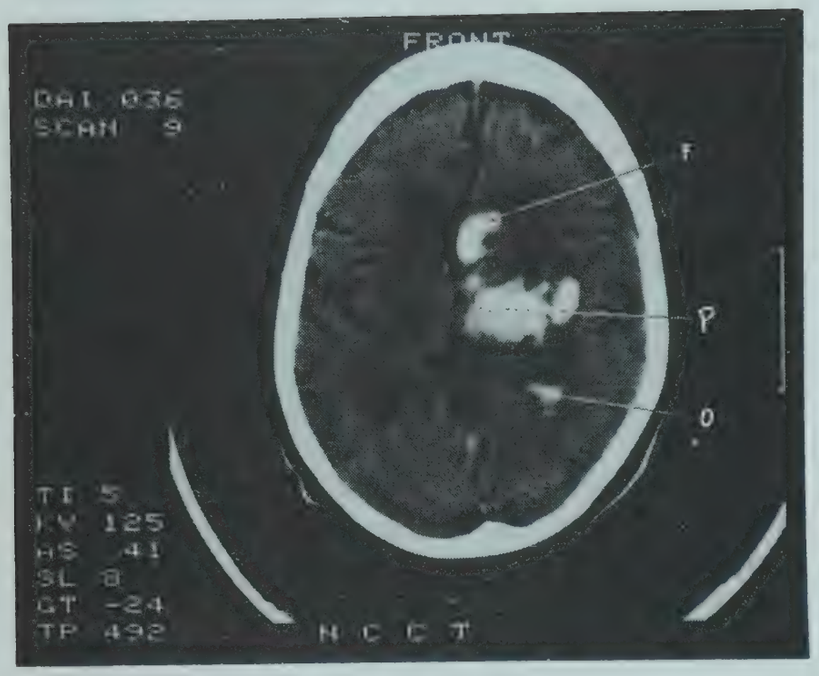


Fig 9.14 The CT scan shows a right putaminal hemorrhage (P) with intraventricular extension; blood is seen in the right frontal horn (F) and occipital horn (O)

Pathology The extravasated blood clots rapidly. Within 48 hours of the hemorrhage, macrophages begin to phagocytose the blood clot. In about 8 weeks, all that remains is a slit-like cavity lined with scar tissue. The hemoglobin pigment undergoes progressive changes from deoxyhemoglobin to methemoglobin and then hemosiderin. Each of these substances has a characteristic MRI appearance which is helpful in dating the hemorrhage.

Clinical features Intracerebral hemorrhage is suspected (rather than an ischemic stroke) if the onset is over a few minutes, there is associated headache and vomiting, marked elevations in blood pressure are noted, or if a characteristic clinical syndrome is present. However, many hemorrhages do not present with any of

Table 9.11 Clinical features of intracerebral hemorrhages

Site	*Symptoms and Signs*
Putaminocapsular hemorrhage	Contralateral hemiplegia, eyes deviate away from the side of hemiparesis, dysarthria may be present
Thalamic hemorrhage	Contralateral hemiplegia and hemisensory loss, transient mutism, dysphasia or dysarthria, visual field defects may be seen. Extension into upper midbrain may cause a variety of eye signs including Horner syndrome and Parinaud syndrome.
Pontine hemorrhage	Deep coma, quadriplegia, pinpoint pupils, absent oculocephalic reflex (doll's eye movements). In late stages, there is cardiorespiratory instability with central neurogenic hyperventilation, apneustic breathing, hypertension or hypotension, and bradycardia
Cerebellar hemorrhage	Vomiting, inability to walk or stand, occipital headache; later there may be ipsilateral sixth and seventh nerve involvement, skew deviation, dysarthria and dysphagia; finally brainstem compression results in coma
Lobar hemorrhage	Headache, deficits characteristic of lesions in the affected lobe

these features and cannot be differentiated from an ischemic stroke in the same anatomical location. Ocular signs are the single most useful method of clinically localising the site of hemorrhage. These have been discussed in the section on coma and are summarised below in Table 9.11.

Investigations A non-contrast CT scan is the investigation of choice for an acute intracerebral hemorrhage and almost always detects a hemorrhage if one is present (Fig 9.14). As time elapses, the blood clot gradually becomes isodense with the surrounding brain parenchyma (1–3 weeks) and later hypodense. During the isodense period, a non-contrast CT scan may fail to detect it unless there is displacement of adjacent structures ('mass effect'). A contrast-enhanced CT scan done at this stage will show a non-enhancing area (the clot) surrounded by a rim of enhancement. An MRI may be done if the patient is stable and several days have elapsed since the hemorrhage. It may detect an arteriovenous malformation if there is one. Because an MRI can date a hemorrhage, it is a useful investigation if rebleeding or extension of hemorrhage is suspected. Finally, a small pontine hemorrhage may be missed on a CT scan but may be detected with an MRI scan. A lumbar puncture should usually not be done if intracerebral hemorrhage is suspected (until a CT scan has ruled it out). If the hematoma is at an unusual site for hypertensive hemorrhage (for example, the temporal lobe), angiography may be done to look for a berry aneurysm or arteriovenous malformation.

Primary Intraventricular Hemorrhage

Primary intraventricular hemorrhage presents with sudden loss of consciousness and few focal signs. If the patient recovers, there are few, if any, residual deficits. Hydrocephalus may occur secondary to ependymitis.

Management of hemorrhagic stroke The basic principles of treating a hemorrhagic stroke are:

1. *optimise cerebral perfusion by stabilising the blood pressure.* The principles are the same as for an ischemic stroke.
2. *reverse a bleeding diathesis, if one is present.* This may involve stopping an anticoagulant such as heparin, streptokinase or tissue plasminogen activator being given to treat an underlying illness. To restore normal coagulation, specific factor transfusions may be given, for example, factor VIII in hemophilia. If the factor is not known or not available, fresh frozen plasma or cryoprecipitate may be given. Protamine sulfate may be given to reverse the effect of heparin.
3. *prevent herniation by decreasing the mass effect.* This may involve surgical removal of the 'mass'. Mannitol should not be given for controlling raised intracranial tension due to hemorrhage, as this may increase the risk of an extension of the bleed. *Surgical removal of a clot is indicated in most patients with cerebellar hemorrhage, subdural or extradural hematoma and should be done as soon as possible.* In pontine hemorrhage, surgery is impossible because of the proximity of the clot to vital support centres. In hemorrhages into the basal ganglia or thalamus, the role of surgery is uncertain. It is a difficult specialised surgery and techniques such as stereotactic removal and endoscopic removal from within the lateral ventricle have been tried. Awake patients with a hemorrhage less than 3 cm usually recover without surgery. Unconscious patients with large hemorrhages (>6 cm) do poorly despite surgery. It should be considered only in medium-sized bleeds, if the patient is awake.

Subarachnoid Hemorrhage (SAH)

Definition SAH occurs when blood enters the space between the pia mater (which closely invests the brain) and the arachnoid mater. Since the subarachnoid space is a continuous space all around the brain, the blood rapidly moves from the site of bleeding to other parts of the subarachnoid space.

Etiology Causes of SAH include traumatic head injury, as well as cerebral hemorrhage. In both cases blood enters the subarachnoid space secondary to bleeding into the cerebral parenchyma. However, the term SAH is usually restricted to primary SAH wherein most of the bleeding is directly into the subarachnoid space. The leading cause of this syndrome is rupture of a saccular aneurysm (*berry aneurysm*) arising from one of the major intracranial arteries. Autopsy studies estimate that 5 per cent of the general population harbour cerebral arterial aneurysms. However, the incidence of SAH is only 1 in 25,000. The second important cause of SAH (which accounts for about 5 per cent of SAH) is rupture of an arteriovenous malformation. This discussion is restricted mainly to SAH due to a ruptured berry aneurysm.

Pathology Approximately, 85 per cent of saccular aneurysms occur in the *circle of Willis* anterior to the posterior cerebral arteries. The common sites of these aneurysms are shown in Fig 9.15. Less commonly, aneurysms may arise from the basilar artery. Roughly, 20 per cent of patients have more than one aneurysm but only one is usually responsible for the presenting leak.

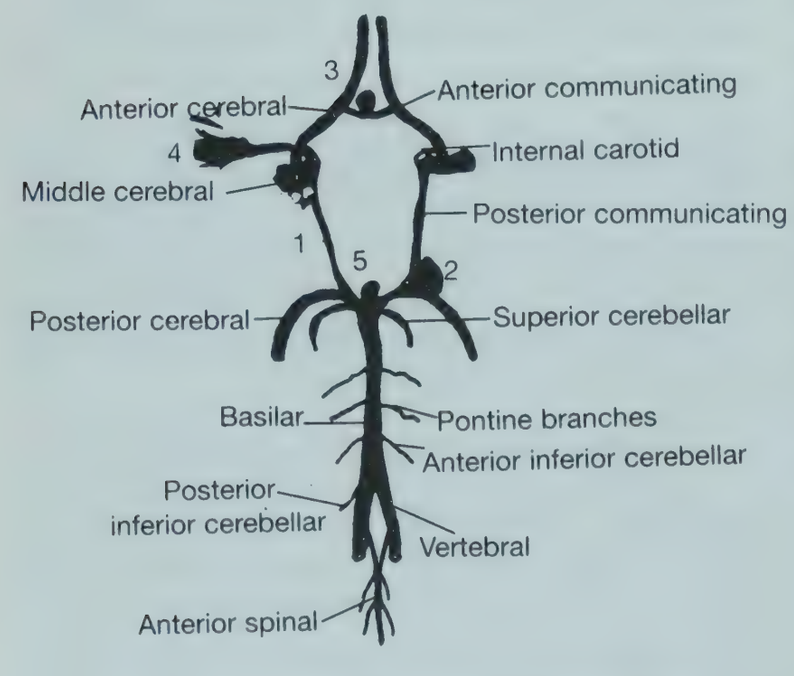


Fig 9.15 Common sites of aneurysmal dilatation
The sites are rated from 1 to 5 with the commonest site marked 1.

An aneurysm arises at a site of congenital weakness in the internal elastic lamina of the artery. Over the years, a dome-like bulge forms at this site connected to the rest of the artery by a narrow neck. Altered flow patterns within this saccular structure may lead to stasis and thrombosis in some areas and thinning of the wall in others. Finally, there is a rupture at the site of thinning. Because there is a great difference between the arterial pressure within the aneurysm and the CSF pressure within the subarachnoid space, blood can rush out rapidly from a small tear. This might result in transient dizziness and even syncope.

The blood irritates the pain-sensitive meningeal structures leading to a diffuse severe headache. Sometimes aneurysms reach a size of over 2 cm without rupture. Such an aneurysm (giant aneurysm) may cause symptoms by its 'mass effect'.[1]

Clinical features Approximately 30 per cent of patients presenting with a SAH recall premonitory headaches in the preceding week (*sentinel headache*). The onset of symptoms is dramatically sudden with explosive headache which may be associated with transient dizziness, syncope or sustained loss of consciousness. The patient is usually drowsy, irritable and photophobic. Neck stiffness is the most characteristic finding but may be absent in the first four hours. Fundoscopy examination may show a subhyaloid (preretinal) hemorrhage, which strongly suggests the diagnosis of SAH. There

[1] The term 'mass effect' is used whenever a pathological structure such as a tumour or an inflammatory mass, occupies some of the limited space within the cranial cavity. Two kinds of symptoms result: compression of the adjoining brain and cranial nerves produces symptoms of localising value. In addition, as the total mass of the intracranial contents increases, there are symptoms of raised intracranial tension.

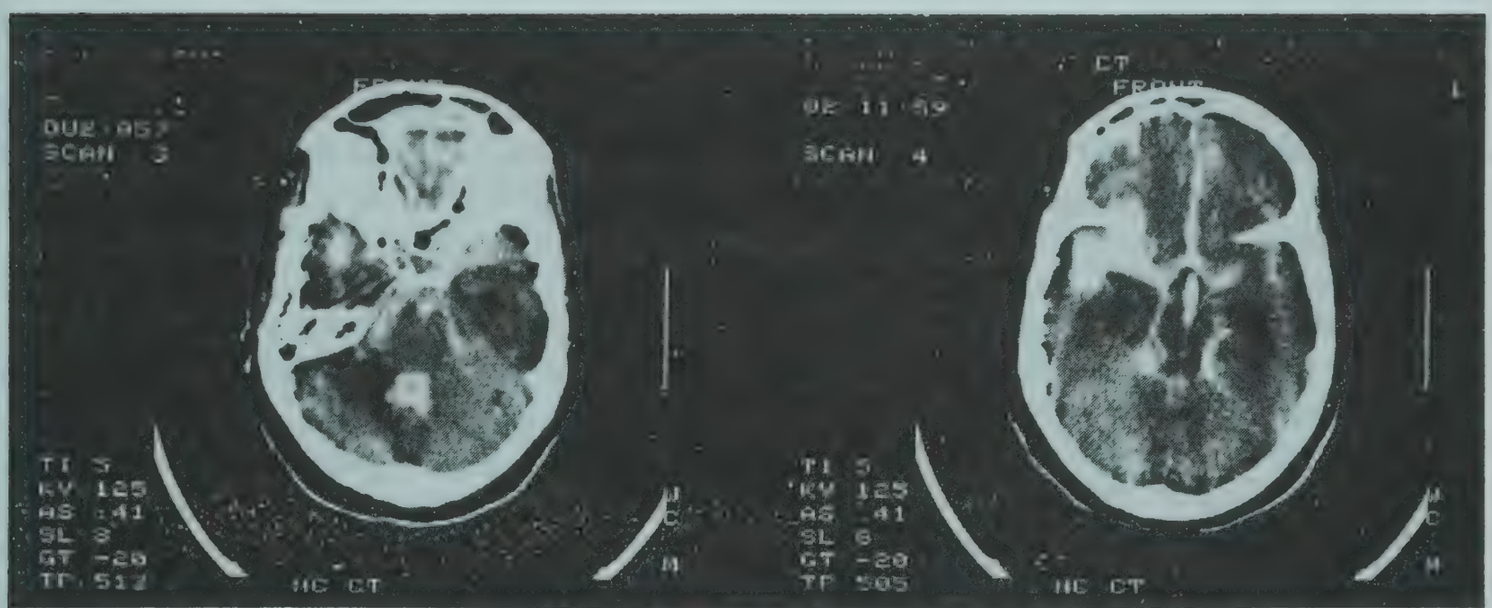


Fig 9.16 These two scans show a hemorrhage into the left sylvian fissure extending into all the subarachnoid cisterns and entering the ventricular system. The picture on the left shows blood in the fourth ventricle. The probable cause is aneurysmal rupture leading to a subarachnoid hemorrhage (SAH).

are usually no focal findings on examination in the acute stage. If an oculomotor nerve palsy is present, this helps localise the site of aneurysmal rupture (to the junction of posterior communicating artery with the posterior cerebral artery). In complicated SAH, there may be focal signs such as hemiparesis because of bleeding into the brain parenchyma or arterial spasm causing ischemic stroke.

The clinical grading of SAH (Hunt's classification) is as follows:

Grade	*Symptoms and signs*
1	Asymptomatic or mild headache
2	Severe headache, neck stiffness
3	Drowsy or confused
4	Stuporose, moderate hemiparesis
5	Deeply comatose, decerebrate rigidity

Diagnosis The CT scan shows subarachnoid hemorrhage in 95 per cent of patients if the scan is done within 24 hours (Fig 9.16). As the time period between ictus and CT scanning increases, the chances of finding blood on the CT diminish. If the CT scan is normal and subarachnoid hemorrhage is suspected, a lumbar puncture is indicated. Differentiation between a traumatic tap and a bloody CSF is done by centrifuging the CSF; the supernatant will be *xanthochromic* in SAH. In the first few hours, CSF xanthochromia may not be visible to the naked eye but blood pigments can be detected on spectrophotometry.

Angiography is performed to localise the bleeding aneurysm. If surgery is not being considered, an MR angiogram (MRA) may be sufficient but a conventional angiogram or digital subtraction angiogram are superior.

Management 1. *Prevention of further hemorrhage/rebleed*: Patients with SAH have a 10 per cent chance of suffering a second bleed within the first 24 hours, 30 per cent chance within the first month and 50 per cent chance within the first year. Early rebleeding is associated with a very poor prognosis. Blood pressures should be restored to known

prehemorrhage levels. Analgesics for the headache, a quiet room, a mild sedative/anxiolytic if required, anticonvulsants and prevention of constipation are important in subarachnoid hemorrhage as stress, straining and systemic hypertension can all precipitate a rebleed. Phenobarbital is sometimes used since it has both sedative and anticonvulsant effects. In aneurysmal subarachnoid hemorrhage, awake or drowsy patients (Hunt's grades 1 to 3) should undergo early angiography (digital subtraction angiography if available) to localise the aneurysm responsible for the bleed, followed by surgical clipping of the aneurysm. Aneurysmal clipping is postponed in comatose patients (Hunt's grades 4 and 5) as in these patients, tolerance for surgery is poor. With medical management and if needed, surgical treatment of hydrocephalus (shunting) or hematoma (removal) these patients may recover consciousness and aneurysmal surgery is done at that stage.

2. *Prevention of cerebral vasospasm*: In upto 25 per cent of untreated SAH there may be a spasm of a major artery (resulting in a secondary ischemic stroke) during the second week after the initial hemorrhage. The vessel involved is usually one which is passing through the subarachnoid blood clot and the site of spasm is within the clot. Hence, it has been inferred that spasmogenic factors are released during clot degradation. If aneurysm surgery is undertaken, blood and clots are removed from the subarachnoid space to the extent possible. In addition, nimodipine (oral, nasogastric or i.v.) at a dose of 60 mg every 4 hours significantly reduces the risk. Any factor which impairs cerebral perfusion increases the risk of cerebral vasospasm; therefore, proper hydration should be maintained (atleast 3 litres of intravenous fluids per day), sodium supplemented, and blood pressure maintained/controlled.

3. *Hydrocephalus*: 15 per cent of patients with SAH develop hydrocephalus. This manifests acutely as a deterioration in sensorium and subacutely as gait disturbance, hypobulia and incontinence. Early hydrocephalus may improve spontaneously. Ventricular shunting procedures may be required for subacute hydrocephalus. Because SAH is a treatable condition requiring skilled neurosurgical techniques, awake patients with suspected SAH should be transferred as fast as possible (after excluding meningitis) to a hospital with skilled neurosurgical facilities.

Arteriovenous Malformation and Cavernous Angioma

The term *angioma* is used to describe a tangled group of structurally abnormal blood vessels. Within the brain, there are two categories: the arteriovenous malformations (which form an abnormal communication between the arterial and venous systems) and the cavernous angioma (which is a cluster of veins without any arterial feeders).

Arteriovenous malformation

In this malformation there are large arterial feeders on the surface of the brain which dip into the parenchyma and divide into a mass of thin-walled, fragile, connecting vessels leading to large draining veins. Because these malformations are similar to arteriovenous fistulae, large volumes of blood course through them at high pressures. The malformations characteristically extend from the cortex to the ventricle in a wedge shape. A familial predisposition is known.

The clinical presentation may be as headache, seizures, a chronic neurologic deficit (because the malformation steals blood from adjacent tissues) or an intracerebral parenchymal bleed. There may be signs of raised intracranial tension. If the vein of Galen enlarges because it drains the malformation, there may be secondary obstructive hydrocephalus. On examination, clues to the diagnosis include a bruit over the skull (25%), and presence of hemangiomas in the retina or over the face

(*Sturge-Weber syndrome*). Investigations include an X-ray of the skull (crescentic or railroad track calcification), a contrast-enhanced CT scan and an MRI, the latter being more specific. Cerebral angiography is required before surgery.

Treatment consists of surgery, if the location is favourable. The purpose of surgery is to reduce the risk of rebleeding (3% per year). If the malformation is deep, other modalities include endovascular embolisation and proton beam irradiation.

Cavernous angioma

The bloodflow within these malformations is slow, and serious hemorrhage is far less likely. They may be asymptomatic or result in headaches. Because of the low flow rates they may not be seen on contrast-enhanced CT or even on a cerebral angiogram. MRI is the most sensitive investigation. Careful follow-up may be sufficient. If the lesion is superficial, surgical excision is easy.

Hypertensive Encephalopathy

Hypertensive encephalopathy is a clinical syndrome of acute onset, where accelerated hypertension is associated with symptoms and signs of neurologic dysfunction. The diagnosis should be considered if the patient presents with headache, vomiting, confusion or coma and a blood pressure reading of >200/130 mmHg (systolic/diastolic). Seizures and focal neurologic signs may be present. The fundus will show grade 4 hypertensive changes (papille-dema, exudates and hemorrhages) and there may be evidence of organ damage elsewhere, such as in the heart or the kidneys. If the patient is not a known hypertensive, it is important to exclude acute renal failure, eclampsia, and other causes of secondary hypertension.

Pathologically there is diffuse brain swelling which may result in fatal herniation, usually of cerebellar tonsils. Hence, lumbar puncture is contraindicated. On microscopic examination of the brain, there may be multiple small infarcts, clusters of microglial cells and necrosis of the arterioles.

Treatment is aimed at lowering blood pressure over a period of 24 hours but not below 150/100 mmHg (systolic/diastolic). This is one situation where intravenous sodium nitroprusside (0.5 μg/kg/min i.v. fusion) and sublingual nifedipine may be used cautiously. Phenytoin as an anticonvulsant and dexamethasone (4 mg q 6 hours) as an antiedema measure may be used. The patient's regular oral antihypertensive therapy should be optimised.

KEY CONCEPTS

Ischemic stroke

- *Atherosclerosis* is the most common cause. Hypertension, diabetes, smoking and hyperlipidemia are risk factors. Less common causes include *emboli* (cardiogenic: rheumatic valvular heart disease, atrial fibrillation, coronary disease, endocarditis, myxoma), *hypotension, arteritis* and *hypercoagulable states.*
- Symptoms depend on the territory involved:
  - *middle cerebral artery*; superior division: contralateral hemiplegia, with arm weakness>leg weakness, deviation of eyes towards lesion, Broca's aphasia
  - *anterior cerebral artery*; weakness and sensory loss with leg involvement > arm
  - *posterior cerebral artery*; contralateral homonymous hemianopsia, alexia without agraphia
  - *basilar artery*; coma with decorticate or decerebrate posturing
  - *vertebral artery*; vertigo, ataxia, Horner syndrome, crossed paralyses
- Progression occurs over the first 48–72 hours. A CT scan at 48 hours demonstrates an infarct better than an immediate CT scan.
- There is acute mortality of about 30%. Manage ment includes supportive nursing care (prevent bed sores, pneumonia, deep venous thromboses; adequate nutrition, fluid electrolyte balance), control of blood

pressure. Low dose aspirin is beneficial in acute ischemic stroke. The role of regular and low molecular weight heparin is at present under investigation. Consider anticoagulation in embolic stroke and progressive basilar artery thrombosis. Rehabilitation must be commenced within days to avoid contractures. Speech therapy is important.

Lacunar infarction

- Infarction of small penetrating branches of the cerebral arteries; these infarcts are usually related to chronic systemic hypertension and are located deep in the hemispheres, pons or internal capsule.
- Typically, lacunar infarcts present as one of three syndromes depending on the site: *pure motor hemiparesis* (internal capsule), *pure sensory stroke* (thalamic) or *clumsy hand–dysarthria syndrome* (pontine lesion). Multiple infarcts can occur resulting in *pseudobulbar palsy.*
- Diagnosis is clinical and a CT scan is confirmatory.
- Management includes supportive care, control of hypertension, and rehabilitation.

Transient ischemic attacks

- There is focal neurologic deficit, with recovery in less than 24 hours.
- Usual etiologies include cerebral emboli from aortic or carotid atherosclerotic plaques. Intra- and extracranial atherosclerosis, hypertension and diabetes are risk factors.
- *Carotid TIAs* present with monocular loss of vision, upper extremity weakness, clumsiness and dysphasia. *Vertebrobasilar TIAs* present with two of the following four symptoms: unsteady gait, vertigo, diplopia, dysphagia, dysarthria.
- A carotid Doppler ultrasound or MR angiography is useful in detecting disease of the carotids. A CT scan is helpful in the acute stage in excluding a progressive stroke or an established ministroke.
- Heparin is useful in the acute stage with a switch to oral anticoagulants subsequently. Choices for long- term therapy include oral anticoagulants, aspirin or ticlopidine. Consider endarterectomy if carotid stenosis is >70%. EC-IC bypass has been shown to be of no use.

Intracerebral hemorrhage

- Usually related to chronic hypertension and resultant *lipohyalinotic* changes in the vessel wall. Common sites are putaminal (50%), thalamic (20%), pontine (15%) and cerebellar (15%).
- Hemorrhages tend to be single, large and catastrophic in onset. Vomiting is a common accompaniment.
- Symptoms depend on the site. Pontine hemorrhage is often characterised by coma at onset, pinpoint pupils and quadriparesis. Putaminal hemorrhage leads to a motor syndrome (hemiparesis) while thalamic hemorrhage results in a hemisensory stroke. Cerebellar hemorrhage manifests as unsteadiness of gait, skew deviation of the eyes and progressive coma lasting over 12 hours.
- A CT scan is the investigation of choice; hemorrhage appears as an area of hyperintensity.
- Treatment consists of supportive care, control of blood pressure. Avoid mannitol or anticoagulants. Consider surgical decompression for cerebellar hemorrhage if the patient is not comatose.

Subarachnoid hemorrhage

- The most common cause is rupture of an intracranial *berry aneurysm* of the circle of Willis. The second most frequent cause is an intracranial arteriovenous malformation.
- Clinically characterised by catastrophic onset of headache. Neck stiffness is absent at onset but develops over a few hours. There may be a history of prior headaches (*sentinel headaches*). The presence of a *subhyaloid retinal hemorrhage* is suggestive. A third cranial nerve palsy suggests an aneurysm in relation to the posterior communicating artery. Complications include *vasospasm* and *hydrocephalus.*
- A CT scan obtained in the first 24 hours can usually detect blood in the subarachnoid space; subsequently the diagnosis may be made if the CSF examination detects *xanthochromia.*
- Management depends on the degree of coma (*Hunt's classification*). If the patient is awake or drowsy, an angiogram may be obtained in preparation for clipping the aneurysm. If the patient is comatose, management is conservative.

9.5 Epilepsy

A *seizure* is a transient derangement of the nervous system secondary to a sudden, excessive, abnormally synchronous discharge of cerebral neurons. It may manifest as abnormal motor, sensory or behavioural phenomena. *Epilepsy* is a disorder which manifests as recurrent seizures.

Epidemiology Seizures may be secondary to a systemic illness or cerebral illness. One in ten individuals will have a single seizure at some time in their lives. The prevalence of epilepsy is 1% and the incidence is 0.1% in the general population. Seizures may occur at any time of life; periods of high risk include the neonatal period, childhood and pregnancy.

Classification A detailed classification of seizure types is provided by the International classification of epileptic seizures' (Table 9.12). Seizures can be classified as *focal* or *generalised.* Focal or partial seizures begin with the activation of the neurons in a single cortical area. The clinical manifestations vary depending on the part of cortex involved. Focal seizures may be motor, sensory or psychomotor. Psychomotor seizures are a common type of partial seizures in adults. They arise from the medial temporal cortex (or in rare cases, the frontal cortex) and manifest as abnormal sensations, feelings, behaviour patterns or autonomic phenomena. These partial seizures are classified as *simple* if the patient retains some awareness of the environment, and as *complex* if there is an alteration of consciousness. Generalised seizures may be bilateral from the onset (*primary generalised seizures*) or may begin as focal seizures which develop into *secondary generalised seizures.* Generalised seizures are always associated with loss of awareness of the surroundings. They are classified depending on the type of motor phenomena seen and the pattern of abnormalities seen on the EEG.

Table 9.12 International classification of epileptic seizures (simplified summary)

Generalised	Absence (typical, atypical)
	Myoclonic
	Clonic
	Tonic
	Tonic-clonic
	Atonic (astatic)
Partial	Simple partial
	Complex partial
	Partial seizures evolving to secondary generalised seizures
Unclassified	

Seizures may also be classified etiologically into those whose cause is largely unknown (*primary* or *idiopathic epilepsy*) and those in whom a structural or metabolic disease can be identified (*secondary* or *symptomatic epilepsy*). Thus, in the classification of epilepsy, secondary epilepsy is used synonymously with symptomatic epilepsy, while secondary generalised epilepsy is used for a generalised seizure which began with

a focal onset. Structural causes usually result in focal seizures while metabolic causes present as generalised seizures.

Persistent, recurrent seizures which last for over half an hour without recovery of sensorium between attacks is a neurologic emergency termed *status epilepticus* and this entity will be discussed separately. The term status epilepticus is usually reserved for tonic-clonic seizures presenting in this fashion. Complex partial seizures can present as status epilepticus and the condition is called *non-convulsive status.* Persistent partial seizures, most commonly partial motor, are called *epilepsia partialis continua.* In this syndrome there may be continuous rhythmic movement of a whole or part of a limb.

Seizures may also be classified according to the triggering factor. Thus, we can have *catamenial* epilepsy related to the menstrual period in women, *photic* epilepsy precipitated by flashing lights and other exotic variants. Such a classification must always be used in conjunction with the descriptive classification given earlier. Thus, one may have primary, generalised tonic-clonic, catemenial epilepsy.

Etiology The causes of epilepsy vary depending on the age at onset. In neonates, common causes are perinatal injury, infections, metabolic disorders and congenital malformations. In children above the age of 2 years, the most common cause is idiopathic epilepsy which appears to be due to complex genetic factors. Infection and trauma are other major causes in this age group. In young adults, new-onset idiopathic epilepsy becomes less common and, therefore, underlying causes should be ruled out. These include neurocysticercosis, head injury, intracranial space-occupying lesions (such as a brain tumour), drug or alcohol abuse, stroke and encephalitis. In adults over the age of 50, idiopathic seizures again become more common. The most common cause of a focal seizure in this age group is a stroke. Other causes listed above should also be considered.

Pathophysiology In health, neighbouring cerebral cortical neurons fire asynchronously. This is because activated neurons inhibit adjacent neurons through collateral inhibitory fibres. The inhibitory neurotransmitter is GABA (gamma-aminobutyric acid). Drugs which block GABA receptors (bicuculline, picrotoxin) provoke seizures in animal models of epilepsy. Excitatory neurotransmitters (acetylcholine, glutamate, aspartate) may also play a role in seizure genesis. During a seizure large groups of adjacent neurons fire synchronously resulting in large spikes which can be recorded over the cortex. Large numbers of neurons show depolarisation (paroxysmal depolarising shift) and bursts of rapid action potential firing. A thalamic generator appears to drive this activity and the widespread nature of thalamic efferents permits the widespread hypersynchrony seen. In focal seizures, a local injury causes membrane instability. If the resultant electrical activity activates the thalamic generator, secondary generalisation occurs.

Clinical evaluation There are two settings in which a patient with seizures may present: either during or immediately following an acute episode or with a history of one or more such episodes in the recent past. These two situations will be discussed separately.

1. *Acute presentation* : The patient may come to an emergency room while having a seizure or immediately thereafter in a confused or comatose state. In either case, the immediate priority is to ensure adequate ventilation, perfusion, and intravenous access. If the patient is experiencing seizures, the next step is to stop the seizures. If she is not having seizures, the examiner needs to determine the cause of the patient's current state which may or may not be the result of a seizure. A careful history from a bystander who observed the episode is most helpful in this regard. If the patient is known to have epilepsy, it is more likely that the episode was a seizure.

In patients who present with a first attack of seizures, an underlying cause must be ruled out. The causes listed under etiology provide an age-appropriate guide. However, almost all the causes listed in an earlier chapter as possible etiologies for coma can present with a seizure. Thus, if a patient has a history of headache for a few days, or confusion or fever prior to the seizure, a central nervous system infection must be suspected. If there is a longer history of headaches or behavioural changes, a brain tumour is likely.

The general physical examination may provide clues such as gingival hyperplasia (long-term phenytoin therapy), stigmata of alcoholism, or skin changes suggestive of a genetic epileptic syndrome (discussed in neurocutaneous disorders). Neurologic examination must be tailored to suit the patient's level of consciousness. Following a primary generalised tonic-clonic seizure, the examination is usually normal, although there may be subtle signs such as confusion or bilateral extensor ('up going') plantar responses. If the patient is on anticonvulsant medication, there may be nystagmus and ataxia. A focal deficit should arouse suspicion of an underlying structural lesion. Once secondary causes have been excluded and the patient's condition has stabilised, investigations to diagnose the epileptic syndrome should proceed in the same fashion as outlined below.

2. *Patient presenting with a history of seizures:*

When a patient presents with a history of seizure-like episodes, the first task is to confirm that the episodes are indeed seizures. They need to be differentiated from other causes of transient neurologic deficits (TIA, migraine) and other causes of loss of consciousness (syncope). Some patients may have seizure-like motor movements not associated with EEG abnormalities. These episodes are called pseudoseizures, are usually indicative of psychosocial problems and should be differentiated from true seizures. Features in the history which suggest true seizures are night-time occurrence (pseudoseizures tend to occur in the day and in front of observers), recumbent posture at onset (cardiac syncope is usually in the erect posture, with the exception of Stoke-Adam's attacks), a definite aura preceding the episode, an injury from falling or tongue bite (in syncope the fall is often more gradual), urinary incontinence and postictal confusion. Postictal confusion is the single feature most suggestive of a true seizure.

Once a seizure is confirmed, clinical localisation is attempted based on the description of the aura (given by the patient) and description of the actual seizure (obtained from witnesses). An *aura* is defined as that part of the seizure phenomenon which is consciously perceived by the patient. An aura does not precede a primary generalised seizure but does occur before a secondary generalised seizure. The aura has a significant localising value. Tingling and numbness suggest an onset in the postcentral gyrus, visual phenomena suggest an occipital focus and vertigo suggests a focus in the superior temporal gyrus. Aura are commonly seen with seizures commencing in the medial temporal lobe (complex partial seizures) and a variety of sensations have been localised to this region. These include olfactory hallucinations (peculiar smells), micropsia and macropsia (objects growing smaller or larger), fragments of conversations, emotions such as anxiety or fear, and visceral sensations (abdominal pain, palpitations). Other symptoms which may constitute an aura of a medial temporal lobe seizure are a dream-like sensation, a sensation that nothing in the surroundings is familiar (*jamais vu*:french for *'never seen'*) or a feeling that what is happening has happened before (*deja vu*:french for *'already seen'*).

The witness is asked to provide a detailed description of what he saw. This is correlated with the descriptions of the different seizure types outlined below. If the history is not

sufficient to identify the type of seizure or a tentative focus, the best course is to obtain a history from additional eye-witnesses, or if the seizures are frequent, proceed with hospitalisation for direct observation of episodes.

Finally, based on the patient's age, seizure patterns (types and frequencies) and associated clinical features, specific epileptic syndromes should be defined. There are several advantages to doing this; the prognosis and treatment may be different and the genetic basis of each syndrome is also thought to be unique.

Partial Seizures

Two common types of partial seizures are *focal motor seizures* and *temporal lobe seizures.* Motor seizures begin with clonic or tonic movements of a specific body part. Areas of the body with large representation in the motor cortex are involved most often. *Jacksonian seizures* begin in one part of the motor cortex (usually the area innervating the thumb) and *'march' serially* to adjacent parts of the ipsilateral motor cortex. Clinically, a typical Jacksonian march begins as a shaking of the thumb followed by a shaking of the entire hand, the forearm, and then the whole upper limb. If the seizure begins with a turning of the head and eyes to one side, these are termed *adversive seizures* and suggest a focus in the opposite prefrontal cortex. If the motor language areas are involved, there may be speech arrest or vocalisations (such as grunts). Temporal lobe seizures manifest primarily as psychic symptoms. The various symptoms described as aura in an earlier section are said to constitute *simple partial seizures* if they occur alone and do not lead to a state of impaired consciousness. In other seizures, these aura are followed by loss of awareness of surroundings and automatisms. Such seizures are called complex partial seizures and last for 1–5 minutes. In a *complex partial seizure,* the patient may show 'staring', frequent blinking, lip smacking, chewing (*simple automatisms*) as well as complex automatisms (which includes bizarre behaviour). During complex automatism, the patient remains capable of complex motor activity such as dressing/undressing, walking or running.

Generalised Seizures

The various subtypes are:

1. Tonic-clonic seizures

These seizures are recognised as epileptic fits by lay persons and by physicians. It was also called *grand mal epilepsy* in the past. In a tonic-clonic seizure, the individual may or may not feel unwell before the onset of the seizure. Such a non-specific feeling of unease is called a *premonition.* There is usually no specific warning symptom (aura). The individual suddenly loses consciousness and falls to the ground. There is a tonic contraction (stiffening) of all muscles, including the respiratory muscles. The latter produces a sudden expiration resulting in an audible cry. Often there is tongue bite or an injury secondary to the fall. The next phase is the *clonic* phase which begins within 30 seconds of seizure onset and can last for a variable period of time, typically 2 to 3 minutes but sometimes much longer. There is rhythmic to and fro movement of all four limbs which gradually decreases in intensity as the seizure subsides. There may be urinary or fecal incontinence, regurgitation of gastric contents or aspiration during this type of seizure. The final phase is the *postictal period* during which the subject gradually returns to normal. The duration of this period varies from 30 minutes to 48 hours and is related to the severity of the preceding seizure. During this period, the individual is drowsy, confused, and often has a headache. Non-focal signs such as bilateral extensor plantar responses may be seen. If the generalised tonic-clonic seizure is secondary, there may be a focal weakness, typically involving the side in which the seizure began. Such focal weakness (called *Todd's paralysis* or *hemiparesis*) is an important clue to the secondary nature of the seizure.

2. Absence attacks

Absence attacks are brief periods of loss of consciousness. The onset of these seizures is almost always in childhood. Two types have been described. The typical or *petit mal absence* manifests as a blank stare which may be associated with simple automatisms and mild loss of muscle tone. It lasts less than 10 seconds and begins and ends abruptly. The other variety carries a poorer prognosis and is called an *atypical absence.* It is similar except for a longer duration and some postictal confusion. Absence attacks can occur hundreds of times in a day.

3. Myoclonic seizures

This is a brief, bilateral jerking movement of the whole body which resembles a startle reflex. There is no associated loss of consciousness. A single myoclonic jerk occurring as a person falls asleep is normal. In myoclonic seizures, however, many such jerks occur, usually shortly after awakening. The jerks may result in falls.

4. Atonic seizures (drop attacks)

These typically begin in early childhood. There is a brief loss of tone. The child's head may drop or the child may fall. A variant occurring in infancy is called the *salaam attack* because of the characteristic movement made by the seated infant.

EPILEPTIC SYNDROMES

Epilepsy is a broad term including a very heterogeneous group of disorders with the common feature of causing seizures. Certain syndromes can be defined based on the age of onset, the type of seizure seen and electro-encephalographic changes. Recognising that the patient is manifesting one of these syndromes is useful in making therapeutic decisions and in prognostication.

Febrile Seizures

Three per cent of otherwise healthy children between the ages of 6 months and 5 years have one or more generalised tonic-clonic seizures associated with fever. The fever is due to a benign cause, commonly a viral cold. It is believed that it is the pyrexia and not the infection itself that provokes the seizure. This syndrome is benign and 95 per cent of affected children have no seizures beyond the age of 5 years. The first episode usually occurs in the child's second year and on the very first day of a febrile illness. Since at this time the diagnosis of febrile convulsions has not yet been established, it is important to exclude a more serious etiology. Features not typical of febrile convulsions are a prolonged duration of seizures (>10 minutes), focal onset, prolonged postictal state and Todd's paralysis. Depending on the index of suspicion for an underlying disorder, a head CT scan, EEG, and lumbar puncture (to exclude meningitis) may be indicated. The convulsion itself may cause mild CSF abnormalities; mild increase in protein and lymphocytes may be present. Management consists of educating the parents to treat minor infections with the antipyretic paracetamol. Starting an anticonvulsant drug when the child becomes febrile is not useful as adequate blood levels will not be achieved. In a few children who are at high risk (premature infants or children with a history of perinatal insult), phenobarbital at a dose of 3–5 mg/kg/day is administered as a prophylactic agent until the child turns five.

Petit mal Syndrome

Ten per cent of childhood epilepsy manifests as very frequent *petit mal* absence attacks in an otherwise normal child. A few of these children will also have myoclonic and generalised tonic-clonic seizures. The EEG pattern during the attacks is characteristic. There is an abrupt onset of generalised 3 Hz spike and wave pattern which ends abruptly at the end of the attack. The EEG appears normal between these episodes. Most children will spontaneously improve after puberty. Treatment consists of sodium valproate. The therapeutic response is excellent and the

child's poor performance at school (which may be the presenting symptom) often improves dramatically.

Lennox-Gastaut Syndrome

This is a rare symptom complex where the child has frequent hard-to-control seizures. Some are absence attacks but the EEG record shows that these are atypical absences (not associated with 3Hz spike and wave pattern). Other seizure types are drop attacks, myoclonic seizures and generalised tonic-clonic seizures. *Salaam* attacks may have been present in infancy. The child is developmentally retarded. Treatment is with sodium valproate. A high fat, low carbohydrate (ketogenic) diet had been tried. The prognosis is poor.

Juvenile Myoclonic Epilepsy

This syndrome begins with myoclonic seizures in the adolescent years. There are associated but less frequent generalised tonic-clonic seizures which are often the presenting syndrome. On specific questioning, the history of early morning myoclonic jerks is elicited. The EEG is characteristic with 2–3 spikes followed by a wave (polyspike and wave discharge at a frequency of 3–6 Hz) before each myoclonic jerk. Treatment consists of sodium valproate which is effective. Patients gradually outgrow their seizures.

Benign Rolandic Epilepsy

This is the commonest epileptic disorder of late childhood accounting for 25 per cent of children presenting with generalised tonic-clonic seizures and a normal neurologic examination. The age of onset is 3–13 years. Most seizures are nocturnal. Daytime episodes may show a focal onset (speech arrest or facial weakness) with secondary generalisation. This syndrome shows an autosomal dominant inheritance pattern. The EEG pattern is characteristic with central spikes (over the rolandic area) on the interictal recording (between seizures).

Mesial Temporal Sclerosis

This is the commonest cause of idiopathic, poorly controlled epilepsy in young adults. Fifty-five per cent of all seizures in adults are complex partial in type. Eighty per cent of complex partial seizures arise from the mesial temporal lobe, that is, the area around the uncus, amygdala and hippocampus. A clinical description of these seizures has been outlined in this section. There may be a history of febrile seizures as a child. In any case, seizures typically begin at about the age of ten and at this time respond well to medication. After a remission of several years however, disabling complex partial seizures begin which are poorly responsive to drugs. Isolated auras may occur. In the interictal period the neurological examination and cognitive examination are normal, or nearly so. On the EEG, ictal and interictal abnormalities are localisable to the temporal lobe. An MRI shows a small, sclerotic hippocampus on one or both sides. Surgery is effective in many of these patients who should therefore be referred to a specialised centre for further evaluation.

Rare syndromes include *Rasmussen syndrome* which consists of childhood onset focal encephalitis, partial motor seizures and progressive neurological deterioration. An antibody to a glutamate receptor may play a role in the pathogenesis of this disorder. The prognosis is poor. Hemispherectomy may prevent further worsening. Another rare syndrome is the *Landau-Kleffner syndrome* where a young child progressively loses language functions (epileptic aphasia). The EEG shows that the period of slow wave sleep is very abnormal being entirely replaced by continuous seizure-like discharges. The prognosis is poor but spontaneous improvement may occur at adolescence.

Investigations Blood tests should include cell counts and a peripheral blood smear. Serum biochemistry is performed to look for abnormalities in blood glucose or electrolytes.

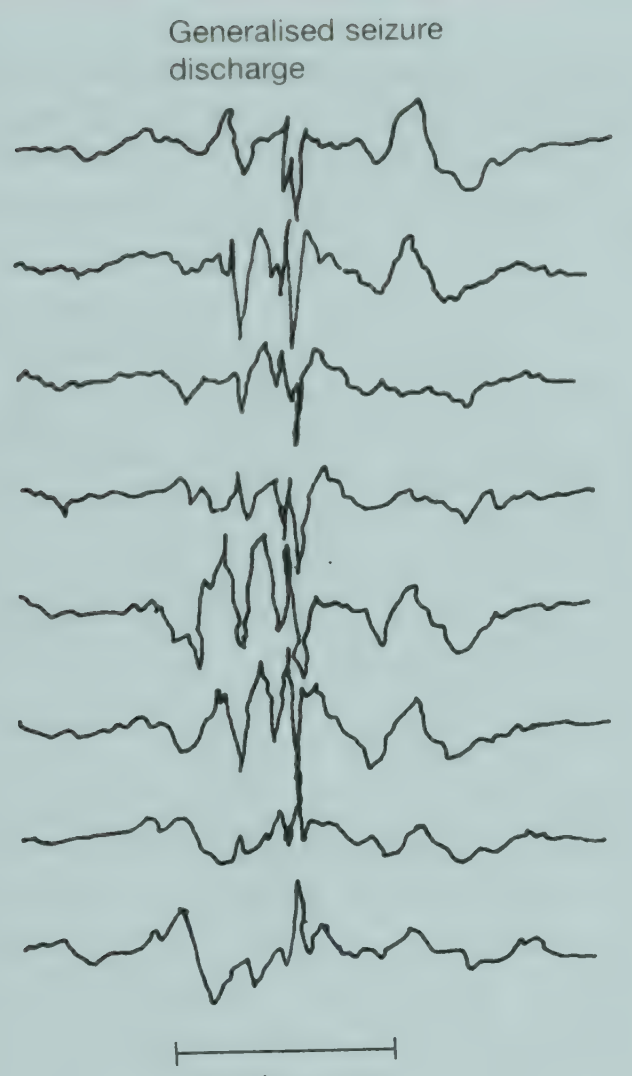


Fig 9.17 EEG in epilepsy

If the patient is already on anticonvulsant medication, blood may be drawn for drug level to check compliance.[1] Lumbar puncture is indicated if meningitis or encephalitis is suspected as the cause of the seizures. Minor CSF abnormalities (a mild increase in cell count and protein) may be present as a consequence of the convulsion and may persist for 48 hours after the convulsion.

The EEG is an essential part of the evaluation of any patient presenting with seizures or suspected seizures (Fig 9.17). When the diagnosis of a seizure is in doubt and an EEG can be obtained soon after the suspected episode, the presence of postictal changes (diffuse slowing following a generalised tonic-clonic seizure) strongly suggest that the episode was a seizure. If the patient has frequent attacks, an attempt is made to capture an ictus while the patient is undergoing an EEG. If seizure discharges[2] are simultaneously visualised on the EEG, the epileptic nature of the ictus becomes clear (Fig 9.17). This is particularly useful in absence attacks. If the episodes are less frequent, video-EEG monitoring or ambulatory EEG may be performed to increase the period of observation.

Despite all efforts, in most patients it is very difficult to actually record a seizure on the EEG. Instead, what is recorded is an *interictal* EEG (between episodes). The presence of *sharp wa es* (high voltage slow waves) or *spikes* (similar to sharp waves but having a duration of less than 70 milliseconds) on the interictal EEG record increases the possibility that the episodes under consideration are seizures. It does not, however, confirm the diagnosis since 1 per cent of the 'normal' population may show occasional spikes or sharp waves on the EEG. If these abnormalities 1) occur repeatedly in the EEG record, 2) always arise from one part of the brain, and 3) are associated with a slowing of the background alpha activity in the same area, they are likely to be pathological. A normal EEG (or even two) does not rule out a diagnosis of epilepsy.

To increase the chances of recording an abnormality, initiation of anticonvulsant therapy (if the patient is not on anticonvulsants) may be delayed until after the EEG. Another method of increasing the diagnostic yield of an EEG is to supplement the conventional awake EEG with

[1] Drug levels are checked if the seizure recurrence is unexpected. In patients known to have poorly controlled epilepsy despite adequate therapy, drug levels need not be repeated each time there is a seizure.

[2] During a seizure the background rhythm changes over a few seconds (recruiting rhythm) finally resulting in high amplitude spikes or spike and wave patterns.

additional recordings during a number of *activating* procedures. The patient is asked to hyperventilate (breathe as rapidly and as deeply as possible) for 3 minutes. The resulting alkalosis may activate seizure discharges. A stroboscope is placed over the patient's face and a powerful light flickers in front of his eyes. The flicker frequency is gradually increased from 5 per second to 20 per second. Normal individuals may show changes in the EEG pattern called *following response* and *photomyoclonic response.* In epileptic patients, the seizure discharges may be precipitated. This response is called *photic driving* and this type of epilepsy is called *photosensitive epilepsy.* Recording an EEG during sleep also increases the chances of finding an abnormality. The patient is often asked to come in a 'sleep-deprived state', that is, having slept 2–3 hours less than usual on the previous night. Finally, the use of special EEG leads (*sphenoidal, nasopharyngeal, nasoethmoidal*) makes it more likely that one will record discharges from the medial temporal lobe. Of these, the sphenoidal electrode is most often used. A long needle electrode is introduced percutaneously to lie adjacent to the foramen ovale.

The EEG is also used to help classify seizures and to define epileptic syndromes. The finding of focal abnormalities in a patient whose seizures appear generalised from the beginning raises the possibility of secondary generalisation. Typical and atypical absence seizures can be differentiated from each other and from complex partial seizures.

Any adult patient presenting with an unexplained seizure should have an imaging study to exclude an underlying structural lesion as the possible etiology. A CT scan (plain and with contrast) is commonly used for this purpose. In a patient with partial complex seizures, an MRI is more likely to detect underlying abnormalities (commonly, mesial temporal sclerosis and, rarely, a tumour in the same region). In patients being evaluated for surgery, a PET scan with ^{18} fluorodeoxyglucose will demonstrate an epileptic focus in 70 per cent of patients as an area of diminished interictal glucose uptake and increased ictal glucose uptake.

Treatment Management of epilepsy involves educating the patient and his family, and teaching the patient to avoid precipitating factors and dangerous situations. A positive outlook should be emphasised. Epilepsy is common and in most patients easily controlled. Most patients have a normal IQ. Marriage, normal sexual relations and childbearing are possible. Apart from a few high risk occupations (flying, professional driving, working at construction sites or with heavy machinery) most jobs can be handled with little risk to the patient or others. It is usually a good idea for the family and close friends to be aware of the patient's condition. If seizures are frequent the teacher and coworkers should be informed so that they are aware of what needs to be done. If a patient has a generalised tonic-clonic seizure, she may be gently lowered to the floor but should not otherwise be moved (unless she is in a dangerous location such as the middle of a road). Hard, hot or sharp objects in the vicinity, on which she could hurt herself as she convulses, should be removed. No attempt should be made to force the mouth open or put anything in it. Once the seizure is over, the patient should be rolled over to one side to clear the airway of secretions. If the patient's colour, breathing and pulse are normal at this point and if she is a known epileptic and recovers consciousness over the next 10–15 minutes then all that is required is to let the patient rest for a few hours. If there is a suspicion of a head injury, a doctor should be consulted. The patient should not be overprotected and moderate exercise is beneficial. Driving alone, cooking over an open fire and swimming alone are to be avoided. Sleep deprivation, hypoglycemia, alcohol withdrawal, cocaine, some prescription medications and above all poor compliance with the therapeutic

regimen can precipitate seizures. The mainstay of therapy is antiepileptic medication.

Antiepileptic drugs Antiepileptic or anticonvulsant drugs are effective in reducing or eliminating seizures in most patients. There are six conventional antiepileptic agents.

Phenytoin, carbamazepine, phenobarbital and primidone are effective against generalised tonic-clonic, simple partial and complex partial seizures. **Sodium valproate** is a broad-spectrum anticonvulsant which is useful in controlling all types of generalised seizures (generalised tonic-clonic, myoclonic, absence and atonic) but is less effective than the other four drugs in controlling partial seizures (simple partial or complex partial). **Ethosuccimide** is effective for absence attacks but is usually used only if sodium valproate is contraindicated in a given patient. Less commonly used agents are: clonazepam which is effective against absence attacks and myoclonic seizures, ACTH which is used to treat a few, rare, poor prognosis syndromes such as West syndrome, and the benzodiazepines, diazepam and lorazepam, which are only used in the treatment of status epilepticus.

The commonly used drugs will be discussed below and then the principles of antiepileptic drug therapy will be discussed. The commonly used antiepileptic medication have been listed in Table 9.13.

The side effects of antiepileptic medication are of two kinds: dose-related side effects common to all the medications and drug-specific side effects. The adverse effects common to all agents are nystagmus, diplopia, ataxia, mild cognitive impairment, and mild teratogenic effect. In therapeutic doses, all drugs can cause gaze-evoked nystagmus which is asymptomatic. At toxic doses, there may be diplopia, dysarthria, difficulty in performing the finger-nose test and cerebellar gait ataxia. Although all antiepileptic drugs can be teratogenic, the vast majority of women taking these medications have healthy babies and uncontrolled epilepsy is far more dangerous to the fetus than any of the medication. Most agents cause mild facial dysmorphism. The incidence of neural tube defects is higher, especially with sodium valproate.

Phenytoin can cause gingival hyperplasia which is best avoided by maintaining good dental hygiene. Less common side effects are hirsutism, coarsening of facies, megaloblastic anemia, rash, lymphadenopathy, eosinophilia and peripheral neuropathy. Phenytoin has a peculiar pharmacokinetic pattern so that near the optimal blood level, a small increase in dose can result in a large increase in the blood levels leading to toxicity. Hence, beyond 200 mg/day, doses should be increased in 50 mg or smaller increments. In patients having frequent seizures an initial loading dose of phenytoin may be given (15–20 mg/kg). The drug should be diluted in 50 ml of normal saline and be given as a very slow intravenous bolus over 15–20 minutes (<50 mg/ minute). More rapid administration can cause hypotension or cardiac arrhythmia. Intra-muscular administration is not adopted as absorption is erratic and cellulitis may supervene at the injection site.

Phenobarbital can cause sedation or rash (including maculopapular rash, toxic epidermal necrolysis and exfoliative dermatitis)[1]. It is the least expensive of antiepileptic medications. It should not be given to depressed patients as it has been used to commit suicide (by over-dosing). Primidone can cause the same side effects as phenobarbital as well as drug induced lupus.

Carbamazepine should be initiated at a low dose (100 or 200 mg/day) and the dosage should be gradually built up over a period of at least two weeks to avoid dose-related side effects.[1] This drug commonly causes mild leucopenia which is usually asymptomatic. Unless the leucocyte count falls below 3000/mm^3 carbamazepine need not be discontinued. Frequent white blood

[1] Exfoliative dermatitis may also be seen with phenytoin. Although rare, it is a serious side effect and antiepileptic therapy should be changed.

Table 9.13 Commonly used antiepileptic drugs

Drug	*Available as*	*Daily dose*	*Dosing frequency*	*Serum half-life*	*Recommended blood level (ug/ml)*	*Mechanism of action*
Phenytoin (Dilantin, Eptoin)	50 mg, 100 mg; also suspension (100 mg/5ml)	150–400 mg (4–7 mg/kg)	once daily at bedtime	24 h	10–20	Na+ channel, use-dependent block; repetitive neuronal firing is blocked
Carbamazepine (Tegretol)	200 mg	400–1200 mg (20–30 mg/kg)	2–3 times a day	12 h	5–12	
Phenobarbital (Gardenal, Luminal)	30 mg, 60 mg, 100 mg	60–200 mg (3–5 mg/kg)	once daily	96 h	10–40	prolongs chloride channel opening; active metabolite of primidone is phenobarbital
Primidone (Mysoline)	50 mg, 250 mg	750–1500 mg (10–25 mg/kg)	twice daily	10 h	5–15	
Sodium valproate (Depakote, Epilex)	125 mg, 250 mg, 500 mg	750–3000 mg (30–60 mg/kg)	three times a day	8h	50–100	slows 'calcium channel block'

counts are not useful; annual counts are sufficient. Carbamazepine can also cause persistent hyponatremia due to inappropriate secretion of antidiuretic hormone.

Sodium valproate can cause nausea which is the most disturbing side effect and can be minimised by starting at a low dose and giving the drug with meals. Other side effects include increased appetite, weight gain, hair loss and tremors. In children below the age of two it may cause drug-induced hepatitis. In adults a mild increase in liver transaminases (serum SGOT/SGPT) may occur but is not an indication for discontinuing therapy.

Antiepileptic drugs can affect the serum levels of concomitantly administered medications including other antiepileptic drugs. They do this by accelerating (phenytoin, phenobarbital and carbamazepine) or depressing (sodium valproate) hepatic metabolic pathways or by competing for plasma binding sites (sodium valproate). If a patient who is already on an antiepileptic agent is given phenobarbital, the serum concentration of the first drug is reduced. If the new drug is carbamazepine, it increases phenytoin levels but lowers the levels of phenobarbital and sodium valproate. The addition of phenytoin lowers the plasma levels of other anticonvulsants except phenobarbital, the levels of which are increased. Sodium valproate increases serum concentrations of other antiepileptic medication.

Carbamazepine, phenytoin and phenobarbital can reduce the efficacy of oral anticoagulants, oral contraceptives, theophylline, steroids and doxycycline. Hence, sodium valproate has an advantage in a woman using oral contraceptives since it does not compromise contraceptive efficacy. Antacids can decrease the absorption of antiepileptic medication. Isoniazid, cimetidine, propoxyphene (Proxyvon), verapamil, diltiazem and erythromycin can increase the levels of carbamazepine. The first two agents can also increase phenytoin levels and this should be kept in mind when treating patients with tubercular meningitis. Salicylates can increase serum sodium valproate levels.

[1] Carbamazepine activates liver enzymes that metabolise it. Hence the body's capacity to metabolise the drug increases with time.

Principles of drug therapy In most adults with epilepsy, phenytoin is the initial drug of choice. In students and pregnant women, carbamazepine is sometimes preferred because it is thought to have a less marked adverse effect on cognition and to be the least teratogenic. Carbamazepine is two to four times as expensive as phenytoin. Pregnant women or those planning to become pregnant should be given folic acid (1 mg/day) to minimise the teratogenic effect of antiepileptic drugs. Sodium valproate is the drug of choice if the patient has myoclonic seizures or absence attacks in addition to generalised tonic-clonic attacks. Partial complex and myoclonic seizures are rarely seen in the same patient.

Monotherapy with a single chosen agent is preferred and satisfactory seizure control can be seen in two-thirds of patients. The addition of a second agent improves seizure control in 10 per cent but increases toxicity in 90 per cent! This is partly because each antiepileptic agents affects the metabolism of the other as discussed earlier. The doses of the medication should be gradually increased until there is satisfactory seizure control or there are unacceptable side effects. In the latter case, a second drug known to be effective in this seizure type is initiated and once adequate doses have been reached, the first drug is withdrawn. The second drug is then titrated. If none of the first-line drugs can produce satisfactory seizure control at non-toxic doses, the patient is said to have intractable epilepsy, the management of which is discussed later. Most patients are controlled with one drug.

An important question is deciding when to start therapy and when to stop. Typically antiepileptics are started after the patient has had at least two seizures because many patients with a single seizure will never have a second seizure. However, a third will have further

seizures; so if the patient has had an unprovoked seizure (not due to an acute injury), has a family history of epilepsy or is in a work situation where a second attack can be dangerous, some physicians will start drugs even after a single seizure. A diagnosis of epilepsy has serious social and psychological implications; if the diagnosis is in doubt it is better to wait and establish a diagnosis. A trial of antiepileptics for vague spells is *not* a good idea. Drug therapy may be continued lifelong or discontinued after 2 to 5 years *without any seizures.* If the patient cannot become seizure-free (seizures include partial seizures and aura), drug therapy should not be discontinued. If a patient is tolerating the medication, can afford it and does not wish to accept the 30 per cent chance of seizure recurrence after withdrawing medication, therapy may be continued. Factors which are in favour of continuing therapy include a large number of seizures before control is finally achieved, a structural lesion causing the seizures, focal neurological deficits and focal abnormalities on the interictal EEG at the time cessation of therapy is being considered. The drug should be tapered over 3 to 6 months; abrupt cessation of therapy can precipitate seizures or status epilepticus. Most recurrent seizures occur in the first year after the antiepileptic medication is stopped.

The best guide to optimal dosage is the clinical response. Blood levels of antiepileptic drugs should not be routinely obtained. They are unnecessary, expensive and, in inexperienced hands, may worsen control. The so-called therapeutic range is merely an average. A given patient whose seizures are controlled with a serum level that is 'low' does not need an increased dosage; nor does a patient who is free of side effects at a 'high' serum level need a reduction in dosage. Drug levels are estimated if there is a question regarding the compliance or possible toxicity or in patients in whom a new drug or new metabolic state (such as pregnancy) may alter drug metabolism.

Patients with epilepsy should be strongly discouraged from professional driving and should drive a personal vehicle only if they have been seizure-free for at least one year. Patients with uncontrolled epilepsy are legally required to stop driving.

Intractable Epilepsy and Surgery for Epilepsy

Intractable epilepsy is epilepsy which cannot be controlled with the maximum tolerated doses of the standard antiepileptic medications. At this stage management is best left to a neurologist. Patients with partial complex seizures are most likely to fall into this group. Structural lesions such as tumours should be excluded. The use of more than one drug may be tried and newer anticonvulsants (vigabatrin, felbamate, gabapentin and lamotrigine) used as add-on therapy. Surgery is being increasingly used as a therapeutic option for intractable epilepsy. The patient should have a focal lesion identified as the source of the seizure discharges by preoperative monitoring including repeated EEGs, video-EEG and, if required, an electrocorticogram. Invasive monitoring using intracranial depth or subdural electrodes may be required. Imaging studies are undertaken (MRI, PET) to look for a structural lesion at this site (commonly mesial temporal sclerosis) since finding one increases the chances that surgery will be successful. The patient should not be mentally retarded and should have the psychological strength and motivation to cope with the long preoperative, operative and postoperative periods. Testing is done to determine if removal of the planned area will cause a serious speech or cognitive deficit. Finally after surgery, the antiepileptic drugs need to be continued and adjusted as required. Surgery is an expensive option and requires a skilled team of neurologists, psychiatrists, neuropsychologists and of course neurosurgeons. The commonly used operation, resection of the temporal pole, results in significant improvement in seizure control and

quality of life in 60 per cent of patients who can undergo it. In patients with dense hemiparesis due to a structural lesion and recurrent generalised seizures arising from the diseased lobe, hemispherectomy may be useful. Patients with severe drop attacks may benefit from section of the corpus callosum.

Status Epilepticus

Status epilepticus is defined as more than thirty minutes of continuous seizure activity or two or more sequential seizures *without* complete recovery of consciousness between seizures. Status epilepticus presents in several forms; there may be repeated generalised tonic-clonic seizures (*convulsive* status epilepticus), a continuous altered sensorium (*non-convulsive* status or complex partial status epilepticus) and persistent partial seizures (*epilepsia partialis continua*). Of these, convulsive status epilepticus is the most dangerous and the most studied. This entity will be discussed in detail; the other two types are briefly summarised.

Epidemiology and etiopathogenesis Status epilepticus is unfortunately a fairly common medical emergency. Fifty per cent of patients are below the age of 18 years. Also, in 50 per cent of the patients there may not be an existing diagnosis of epilepsy. This is because status epilepticus may occur as a response to an acute cerebral insult. Precipitating causes may include encephalitis, meningitis, cerebral malaria, head injury, stroke, hypoxia, metabolic encephalopathy, drug intoxication or poisoning, alcohol withdrawal, eclampsia, and brain tumours. In patients who are known epileptics, the single most common cause of status is an abrupt discontinuation of therapy. In many patients (particularly those known to have epilepsy), status epilepticus can occur without any apparent precipitating factor.

Management Convulsive status epilepticus is an emergency because the mortality may be as high as 30 per cent in adults. The prognosis is slightly better in children. The longer the duration of the status, the greater the risk of permanent brain damage. The hypersynchronous electrical activity increases the metabolic needs of the neurons (at the same time that the motor convulsions impair systemic oxygenation) which use up blood glucose. This explains our focus in managing a patient, which involves the following steps: 1) stop the seizures, 2) maintain life-support, 3) find and treat the cause, as this may be essential for seizure control, to prevent recurrence and to avert an adverse outcome due to the underlying cause. Therapeutic and diagnostic measures should be conducted simultaneously.

Stopping seizures: If a definite diagnosis of status epilepticus cannot be made based on the history and initial examination, the patient is observed for continuing seizure activity or for any new seizures. If the initial assessment confirms the diagnosis of status epilepticus, an antiepileptic drug should be administered immediately. The drug of choice is diazepam (administered as an intravenous bolus of 10 mg, given over 2 minutes). If the seizures do not stop in 5 minutes, a second bolus of 10 mg may be administered. Some physicians prefer to start with slow administration of a 20 mg bolus, stopping as soon as the convulsive activity begins to abate. Diazepam is highly lipid soluble and quickly enters the brain. However, it is then redistributed to other fatty tissues causing brain and serum levels of the drug to fall. The positive effect of this redistribution is that the patient's sensorium recovers from the sedative effect of diazepam in about 30 minutes. The negative effect of this redistribution is that seizures can recur as drug levels fall. Hence, if the patient is not previously on an antiepileptic drug, an antiepileptic agent should be administered to prevent seizure recurrence. Intravenous phenytoin is usually administered for this purpose, with an intravenous loading

dose[1] as described previously. Thereafter, 100 mg of phenytoin is given intravenously every 8 hours until the patient recovers sufficiently to be switched to oral phenytoin. *Intramuscular therapy has no place in the management of status epilepticus.* If an intravenous line cannot be established, diazepam or paraldehyde (0.1ml/kg) may be administered rectally. Lorazepam (0.1 mg/kg i.v.) has been used instead of diazepam but it is not clear if there is any specific advantage in doing so. If the seizures are not controlled with diazepam boluses or with phenytoin,[2] *refractory status epilepticus* is diagnosed. A neurologist should then be summoned. Treatment modalities include an intravenous 'diazepam drip' (100 mg in 1 unit of 5% dextrose administered over 8 hours) or a 'phenobarbital drip' (20 mg/kg at a rate of 100 mg/minute). Since such intravenous therapy can result in respiratory depression requiring ventilatory support, it is ideally initiated in an intensive care setting. When all else fails neuromuscular paralysis is resorted to, which should be done by an anesthesiologist. A patient in this state should undergo concomitant EEG monitoring to determine if seizure activity has stopped.

Maintenance of life-support: As with any unresponsive patient, the immediate concern is ensuring a clear airway, maintaining blood pressure and circulation, and gaining intravenous access. However, securing an airway and assisting respiration are much easier if the convulsion has been stopped. If this is not possible, oxygen should be administered using a nasal cannula, or using a 'bag and mask' and an anesthesiologist immediately summoned who may intubate the patient after administration of a short-acting neuromuscular blocking agent (which transiently abolishes the movements). If all else fails, a tracheostomy may be done.

Blood should be drawn for a complete blood count, peripheral blood smear (including examination for malarial parasite), serum biochemistry (blood glucose, sodium, calcium, and urea), and for antiepileptic drug levels (where applicable). Urine and blood samples should also be obtained and stored for toxicological screening, if indicated based on the history and examination. ECG monitoring and monitoring of oxygenation should be initiated (using a pulse oximeter or with periodic arterial blood gas analyses).

Hypoglycemia can occur during status epilepticus; therefore, a bolus injection of 50 ml of 50 per cent dextrose solution should be administered intravenously alongwith 100 mg of thiamine.[3] Systolic blood pressure should be maintained at normal levels, using vasopressors if necessary, since a drop in blood pressure can seriously impair cerebral perfusion. In rare situations, a patient may have severe metabolic acidosis requiring intravenous bicarbonate therapy. It should be remembered that over-correction is more likely to precipitate seizures than mild acidosis itself. Body temperature may rise because of the convulsive activity or due to an underlying infection; temperature should be monitored to avert hyperpyrexia. A patient with status should be monitored in an intensive care setting until he returns to a normal sensorium.

Complications of status epilepticus include aspiration pneumonia, and, rarely, rhabdomyolysis and myoglobinuria. Hence, a chest X-ray should be obtained (to look for aspiration pneumonia), and urine output should be monitored during recovery.

Identification of underlying cause and prevention of recurrence A second phase of

[1] Phenytoin should be given in normal saline as it will precipitate in 5% dextrose.

[2] If diazepam controls the seizures, phenytoin is given to prevent recurrence. If diazepam does not control the seizures in 10–20 minutes, phenytoin is still given to control seizures. Doses of phenytoin >30 mg/kg are contraindicated because such high doses may themselves provoke seizure activity.

[3] Thiamine is given in patients with nutritional or alcohol-related thiamine deficiency, the administration of glucose (which requires thiamine for its metabolism) can precipitate acute thiamine deficiency (Wernicke-Korsakoff psychosis).

diagnostic studies is begun as soon as the patient stabilises. The aim is to identify the underlying conditions and prevent recurrence. In any patient (particularly a child) presenting with status epilepticus and fever preceding the status, CNS infection is a major concern and a lumbar puncture should be performed. If a mass lesion is suspected, a CT scan of the head should be obtained prior to the lumbar puncture. Other studies are obtained based on the index of suspicion from the clinical examination and history; these may include a blood 'screen' for drugs and toxins, and a CT scan of the head which is indicated in any adult who does not have a preexisting diagnosis of epilepsy.

Chronic antiepileptic therapy is usually initiated when the status epilepticus is caused by a structural lesion and is continued (and optimised) in patients with preexisting epilepsy. Chronic antiepileptic therapy is not indicated in patients who have status epilepticus solely as a consequence of transient metabolic disturbances (such as hypoglycemia). When status epilepticus is the patient's first seizure and no cause is found, the decision to initiate long-term antiepileptic therapy should be individualised (based on the patient's occupation, family history of seizures and EEG).

Non-convulsive Status

A patient with non-convulsive status presents with altered sensorium or abnormal behaviour (epileptic twilight). The patient has very frequent or continuous complex partial or absence seizures. Complex partial status may occur in a known epileptic. It may also occur as the first seizure in an elderly patient with a tumour or silent infarct. Absence status may occur in a patient who is acually ill with a metabolic disturbance such as hyponatremia. Subtle clues to the diagnosis of non-convulsive status include a waxing and waning of the altered sensorium, fluttering of eyelashes and involuntary lip movements. The differential diagnosis includes an acute psychosis and metabolic coma. Once the diagnosis is suspected it can be easily proved or disproved with an EEG. Treatment commences with diazepam to stop the seizures, and is followed by anti-epileptics to prevent a recurrence. The dangers of uncontrolled non-convulsive status include all the risks of altered sensorium (death due to aspiration, injury). The patient may recover with few sequelae except a period of amnesia.

Epilepsia Partialis Continua

Persistent focal motor seizures, focal sensory seizures and aphasia may occur due to a partial status. The etiology may be a tumour, stroke, viral encephalitis or Rasmussen's encephalitis. A patient with a partial motor status remains conscious unlike a patient with asymmetrical generalised tonic-clonic status who is unconscious; for instance, a patient with generalised tonic-clonic status who also has hemiplegia may only show movements of one side thus mimicking a partial motor status. The patient with epilepsia partialis continua may complain of severe pain and exhaustion. Treatment consists of diazepam and antiepileptic medication.

KEY CONCEPTS

- A *seizure* is a paroxysmal depolarisation within neurons which results in sudden attacks of motor/sensory/behavioural phenomena with or without altered consciousness. The term *epilepsy* is used when there are *recurrent* seizures. *Status epilepticus* refers to the occurrence of incessant seizure activity for >30 minutes, i.e. repetitive seizures without a seizure-free interval.
- *Aura* is that part of the seizure which is perceived by the patient. It is a focal manifestation which indicates the focus of origin of the seizure.
- Seizures may be *partial* or *generalised*. *Partial seizures* begin focally with sensory/motor/psychic phenomena. Partial seizures may be *simple* (some awareness of consciousness) or *complex* (altered consciousness). *Generalised seizures* affect motor function and consciousness from onset.
- *Generalised tonic-clonic seizures* begin with loss of consciousness and tonic muscular contractions followed by clonic jerks. This variety is the most common and most easily recognised. *Absence seizures* are characterised by sudden interruption of activity and a loss of responsiveness for <10 seconds. The patient stares blankly and may make rhythmic facial movements. Onset is in childhood and there is a genetic predisposition. In *complex partial seizures* the patient has a 1–2 minute loss of contact with surroundings during which he performs automatisms (like the smacking of lips). *Myoclonic seizures* refer to brief jerking movements of the body like a startle reflex without loss of consciousness.
- A good history obtained from someone who has witnessed seizure episodes is vital for distinguishing seizures from *pseudoseizures* and for identifying the type of seizure. Nocturnal occurrence, onset during recumbency, history of an aura, injury from fall, incontinence during the episode or postictal confusion suggest a true seizure.
- An *EEG* is the investigation of choice for confirming the diagnosis, classifying seizure type and for defining epileptic syndromes.
- Management consists of counselling, support and antiepileptic medications (for >2 seizures). Monotherapy is preferred in treating epilepsy and medication usually continued until a 2–5 year seizure-free interval is achieved. Phenytoin and carbamazepine are effective in generalised tonic-clonic and partial seizures. Sodium valproate is effective in most seizures, including myoclonic seizures; it has lower efficacy in partial seizures. Drug levels may be obtained if there is concern regarding compliance or an altered metabolic status. Intravenous diazepam drip may be required for the control of status epilepticus. When epilepsy is refractory to medical management, the *surgical* option may be considered.

9.6 Cognitive and behavioural neurology

The neurology of higher mental functions is now a separate branch which does, however, overlap with the realms of psychiatry. The pathophysiology of memory and language disorders will be discussed in this section along with a discussion of dementia. In addition, delirium is discussed in the psychiatry section. Before continuing with this section a review of the localisation of function in the cerebral cortex—'lobe syndromes' as described in an earlier chapter—is suggested.

The Limbic System

There is a horseshoe-shaped rim of cortex surrounding the junction between the diencephalon and each cerebral hemisphere. This rim of cortex, which is phylogenetically older than the rest of the cortex has been called the *limbic lobe*.[1] The structures forming the limbic lobe are the amygdala, the hippocampus, the parahippocampal gyri, the cingulate gyrus and the nuclei of the septal area (at the base of the septum pellucidum). Other structures functionally connected to the limbic lobe include the olfactory area, the hypothalamus including the mammillary bodies, the anterior and dorsomedial thalamic nuclei and parts of the midbrain reticular formation.

Broadly speaking, the limbic lobe receives a variety of external sensory inputs, information about the internal milieu through the hypothalamus and input regarding the state of activation from the reticular formation. It projects through thalamic nuclei to the frontal cortical areas. The functions of the limbic lobe are integrating voluntary cortical behaviour with internal drives such as hunger, and participating in the generation of emotions such as rage. It plays an important role in the storage and recall of memories.

The hippocampal formation lies in the medial wall of the inferior horn of the lateral ventricles. It is divided into three parts: a dentate gyrus, the cornu ammonis (CA regions 1–3) and the subiculum. The hippocampus receives its input chiefly from the cortex in the anterior part of the parahippocampal gyrus, an area called the entorhinal cortex. It projects through the fornix to the mammillary bodies. Lesions in these areas cause amnesia. The entorhinal cortex and the hippocampus suffer severe neuronal loss in Alzheimer's disease. The mammillary bodies are damaged in Wernicke-Korsakoff psychosis.

Memory

Memory is a collective term for the processes by which we record our perceptions of the external world (*registration*), store the concepts we synthesise, and manipulate these stores to enable recall or recognition when we need to. *Recall* is the process by which we spontaneously come up with the answer, while *recognition* is the process by which we are able to pick out the correct answer if two or more choices are offered to us. When we look up an unfamiliar telephone number and then turn to the telephone to dial it,

[1] From the latin word 'limbus' which means 'border'

we retain the number in our memory for only a short period of about 60 seconds. This is registration or immediate recall and depends on the person's ability to be attentive and to concentrate. If we decide that this fact is important, the memory is consolidated in our *short term memory* which refers to our memory for things which happened approximately 1 minute to 30 minutes (often 5 minutes) earlier. This is tested by giving the patient a list of words or a simple story to remember, distracting him with other questions or conversation and then asking him after 5–10 minutes to recall what he was asked to remember. *Long term memory* includes memory for events of the recent past (events of a few hours, days, weeks and months) as well as memory for events of the remote past such as important personal information, general knowledge, and things the patient used to know in relation to his work or other interests. In the process by which memories are transferred from recent to remote memory, some memories are lost but those which are retained appear more resistant to loss than some other recent memories.

Memory may be *declarative* (in which specific facts are brought to conscious attention) or *procedural.* Procedural memory is the process by which a patient subconsciously performs a learned skill such as typing or driving. Declarative memory may be *generic* or *semantic* (a person recognises a dog as a dog) or *episodic* or *specific* (a person recognises a friend by name). In a patient with memory loss due to dementia, declarative memory is lost before procedural memory and specific memory is lost before semantic memory.

Memory loss affecting a single modality is seen with lesions of the concerned association cortex and is called *agnosia.* Thus, a lesion in the visual association cortex causes a visual agnosia where a patient cannot recognise a visually presented stimulus. If an object can be recognised and used appropriately but not named, the defect is called *anomia.* A memory impairment which is pervasive and extends to all sensory modalities is amnesia. Amnesia may be for events before an event (*retrograde* amnesia) or an inability to form new memories (*anterograde* amnesia). A patient with amnesia may make up or imagine events to fill up the gap in his memory and describe in great detail events which never occurred (*confabulation*). What memories are retained also depends on the patient's interests. Memories in certain modalities (visual, verbal, music) may be better retained than others.

Transient global amnesia This is a sudden-onset loss of recent memories and an incapacity to form new memories, and typically lasts for 4 to 24 hours. The patient is aware of her identity and can recognise family members but may not recall what happened over the previous few days (before the onset of the problem). She forgets ongoing events within a few minutes so that she may repeatedly ask the same questions; the patient appears disoriented, confused and distressed by this disorientation. After the episode is over, the patient does not recall any events which occurred during this period. The etiology of these episodes may be vascular.

Language

Language involves all the processes by which members of a species communicate with each other. Speech refers to spoken language. The ability to speak involves an ability to select the appropriate words and connect them in the proper order, to articulate them clearly in a voice which is loud enough to be audible. If the ability to select words and use them is impaired, it is defined as a type of aphasia. Difficulties in comprehending language and using other modes of expression such as writing are also included under the category of aphasia. The presence of aphasia suggests a cortical lesion. A defect in articulation is called *dysarthria* and may be seen with diseases of the basal ganglia, thalamus, and the cranial neuromuscular apparatus. *Dysphonia*

is an impairment in the volume and tone of the voice due to a disease of the larynx or its innervation.

The important characteristics of *spontaneous* speech are its fluency (number of words per minute), content, syntax (the way in which the substantive words such as nouns and verbs are connected by linking words, according to the grammatical rules of the language), and prosody. Prosody refers to the intonation, rhythm and melody which give speech those characteristics which enable us to identify an accent or judge an emotional overtone. Other attributes of speech which should be tested are *repetition,* and the ability to *name objects.* A complete assessment of language should also include assessment of speech comprehension, spontaneous writing, writing to dictation, and reading. It is important to ensure that the patient was able to perform these activities before the ictus. The inability to name objects is called *anomia.* This can be differentiated from agnosia by the fact that the patient can describe the object, use and match it but cannot name it. Subtle deficits may be detected by asking the patient to name parts of an object such as the dial, hands and strap of a wrist watch. The inability to read is called *alexia.* Pure alexia is seen with a lesion involving the dominant (left) occipital lobe and the splenium of the corpus callosum. This isolates the language areas from both visual cortices. The inability to write is called *agraphia.* Pure agraphia is rare, and when present is seen with a frontal lobe lesion. Alexia with agraphia is seen with a lesion of the dominant (left) angular gyrus or as part of Wernicke aphasia.

The clinical characteristics of the most common aphasias are summarised in Table 9.14. *Broca's aphasia* is caused by a lesion in areas 44 and 45 on the dominant side (usually a stroke). In addition to a lack of fluency, the speech seems to be made with considerable effort, is disprosodic, agrammatic (errors in syntax) and poorly articulated. Initially, patients may be mute; later, stereotypic greetings (such as 'hello') return and finally speech returns. *Wernicke's aphasia* (also called central or sensory aphasia) is characterised by a fluency of 100–200 words per minute so that the patient may sound euphoric or schizophrenic. The speech has normal articulation and prosody. However, the substantive words are replaced by incorrect ones so that the speech is incomprehensible. These replacements (*paraphasias*) may be words which are wrongly pronounced (*phonemic* or *literal paraphasias*), or wrongly selected (*semantic verbal paraphasia*), or a newly invented word (*neologism*). For instance, a patient seeing and trying to describe a picture of a telegraph pole may say, The you know delegraph [phonemic error] bus [semantic error] hagenstans [neologism]. While a patient with motor aphasia is aware of his deficit, a patient with a sensory aphasia may be indignant that others are unable to understand him.

In *conduction* aphasia as in sensory aphasia, there is fluency but there are defects in articulation and the patient is aware of her deficit. The characteristic feature of *transcortical* aphasia is the relative preservation of repetition.

Evaluation of Cognitive Status

The areas of cognitive function which need to be examined include the following:

1. whether the patient is awake and if not how he can be aroused (describe stimulus and response);
2. the patient's capacity for sustained attention: one test is the *digit span,* where the patient is asked to repeat a random list of digits (normal digit span is 7 forwards and 5 when the patient has to invert the digits and recite them backwards). Another is asking the patient to spell a 5-letter word backwards. A third is asking him to recite the months of the year or the alphabet forwards and backwards.
3. language should be assessed since testing other cognitive functions is affected by language difficulties.

Table 9.14 Common aphasias

Type of aphasia	*Speech output*	*Comprehension*	*Repetition*	*Localisation (dominant hemisphere)*	*Associated findings*
Global aphasia	very scant, patient may be mute	impaired	impaired	large middle cerebral artery territory infarct on dominant side	right (i.e. contralateral) hemiparesis with hemisensory loss
Motor aphasia (Broca's)	non-fluent (<50 words/min)	intact	impaired	lower posterior frontal cortex	right (contralateral) hemiparesis
Sensory aphasia (Wernicke's)	fluent, even excessive	impaired	impaired	posterior and superior temporal cortex	often none
Conduction aphasia	fluent	intact	impaired	supramarginal gyrus	often none, may have sensory impairment in upper limb or homonymous hemianopia
Transcortical motor aphasia	non-fluent	intact	intact	white matter adjacent to Broca's area	
Transcortical sensory aphasia	fluent	impaired	intact	white matter around Wernicke's area	

4. memory (short term, recent or remote) and orientation (awareness about time, place and person);
5. visuospatial abilities are tested by asking the patient to draw a cube (Fig 9.18), to copy intersecting pentagons, to draw a clock (an early loss is the ability to correctly place the minute hand), to copy a design made with blocks, to distinguish what is missing in a given picture depicting everyday events and to distinguish right from left;
6. *praxis* is the patient's ability to plan and execute a complex motor task such as dressing, undressing or addressing an envelope. It may also be tested by asking the patient to perform a sequential 3 to 4 step task. Apraxia is present if a patient has difficulty in carrying out the task although he understands what is to be done and has adequate motor strength and coordination to do the task. Apraxia restricted to one limb may be tested by asking the patient to wave or salute with that limb;
7. mood and its effect as well as motivation should be tested. Details are discussed in the chapter on psychiatry;
8. initiative is assessed by the patient's general level of interest in the examination. A *hypobulic* patient gives a few, brief responses. He sits still with little spontaneous activity. *Bradyphrenia* is a slowness in responding and is assessed by timing the patient's performance on specific tasks and comparing the performance with age-appropriate and IQ adjusted norms;
9. *insight* is assessed by asking the patient to describe his problem. A patient with diminished insight diminishes the extent of difficulty or denies it. *Judgement* is tested by asking the patient what he might do in a given situation such as finding a purse on the road. *Abstract thought* is assessed by asking the patient to explain common proverbs, testing the capacity to understand the idiomatic use of language and asking the person to describe the similarities and differences between common groups of objects (for example, orange and banana are both fruits);
10. calculation is tested keeping the patient's level of education in mind. Common tests include serial subtraction from 100 (by 7s, by 3s; five correct responses in a row are sufficient to rule out a problem e.g. 100, 93, 86, 79, 72) or problems using money to make change. Many people without formal education can easily answer problems such as how much change will be left after using a ten rupee note to buy 2 kg of brinjal at 3 rupees a kilo.

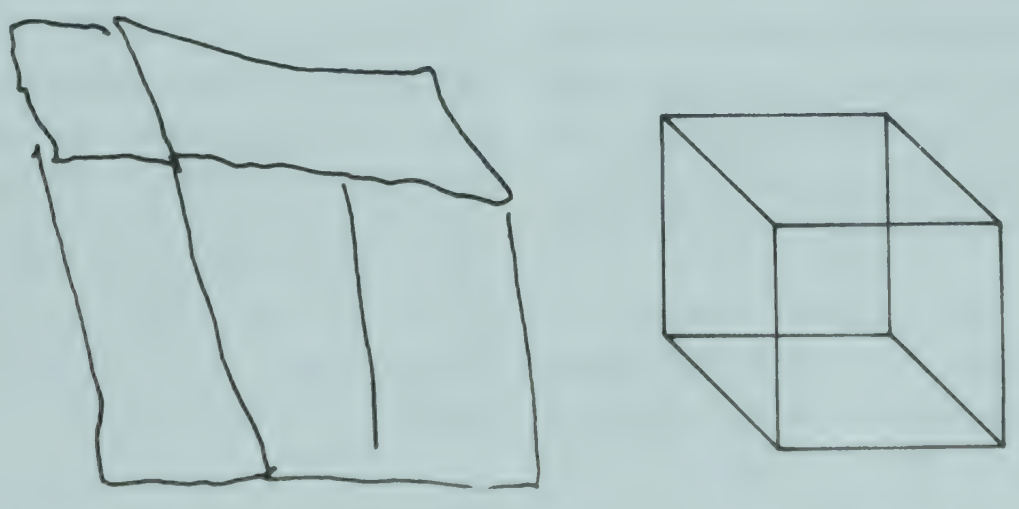


Fig 9.18 Visuospatial impairment: A patient with Alzheimer's disease has tried to copy the cube drawn on the right.

Evaluation of a patient with suspected dementia
The patient's level of education, cultural background and interest must be kept in mind while evaluating his cognitive status. The evaluation of cognitive and behavioural status begins with a detailed history taken from the patient and his family. Sample questions are listed below.

- Does she run the home or her end of things independently ?
- Does she perform adequately at work ?
- Has she given up any hobbies or interests in the past five years or reduced her level of participation in them?

(These questions test the 'executive functions'– initiative, persistence and sequential ordering. Patients with mild dementia may require prompting or specific instructions).

- Has the patient had difficulty with her memory? (for names, appointments, misplaced objects)
- Has the patient had any difficulty in conversing? (not finding the right word, not understanding, repeating questions)
- Can the patient independently handle financial responsibilities and shopping to the extent earlier possible?
- Has there been a change in the patient's mood, thought content or behaviour? (Ask for depression, obsessions, compulsions, hallucinations, delusions, paranoia)
- Have there been changes in the patient's ability to look after himself (bathing, dressing, shaving, feeding) or in the vegetative functions– sleep, appetite (and weight), thirst, bowel and bladder function and libido? Have there been changes in his gait or a history of falls?

On examination the patient's appearance, social interaction, recall of history, insight, mood and effect as well as conversational language abilities are evaluated. This is followed by a brief, formal evaluation. A standard battery such as the Folstein *Mini-mental Status* Examination (MMSE) has the advantage that it is widely used. The technique of doing an MMSE is outlined in Table 9.15. Other sensitive screening tests include asking a patient to draw a clock and show a stated time on it and asking him/her to give a list of words belonging to one category (for example, four-footed animals). If there are specific impairments, these should be explored in greater detail as discussed earlier in this section.

If the patient requires formal neuropsychological assessment the neuropsychologist will decide on an individualised battery which may include the Wechsler Adult Intelligence Scale (WAIS), the Wechsler Memory Scale (WMS) and the Halstead-Reitan battery if the patient has mild dementia. Many of these tests have been developed in the West and have cultural biases. They also require the patient to be literate. Other tests such as Raven's progressive matrices and the Luria figures are less culture- and literacy-dependant. These tests are best learnt by watching someone perform them. In patients with severe dementia there are special scales such as the 'severe impairment battery' which test such functions as recognising a cup or identifying a colour. Structured questionnaires may be administered to the patient to check for symptoms of depression or to a family member to check for behaviour problems.

DEMENTIA

Dementia may be defined as an acquired, persistent impairment of intellectual function with compromise in at least three of the following spheres of mental activity—memory, orientation, language, visuospatial skills, personality and cognition—of a degree sufficient to impair the patient's functioning at home or at work.

Epidemiology The spectrum of normal cognitive function is wide. Hence it is difficult to define dementia except in relation to the *change*

Table 9.15 Mini mental status examination

Questions	*Points*
What is the year?	1
What is the season? (or closest holiday?)	1
What is the month?	1
What is the date?	1
What day of the week is it?	1
Which city are we in?	1
Which district?	1
Which state are we in?	1
What is the name or address of this place?	1
Which floor are we on?	1
I will name 3 objects, listen carefully then repeat them; try to remember them: (any 3 objects e.g. banana, table, book)	3
Spell this word backwards: (a 5 letter word) **or** serially subtract 7 from 100 (5 times)	5
Do you remember the three words I said earlier?	3
Name these : (show two common objects)	2
Repeat this (a phrase with many prepositions/conjunctions)	1
Read and obey (use card with sample phrases like 'Close your eyes.')	1
Call out a 3 step command (e.g. 'Point to the ceiling, then to the floor, then stand up.')	3
Copy this figure (2 intersecting pentagons)	1
Write a sentence.	1

from the patient's previous level of functioning. Eventually all patients with dementia progress to a clearly abnormal state if they live long enough, so time is an excellent (if unsatisfactory) diagnostic aid. The incidence[1] of dementia rises exponentially with age from less than 1 per cent at 60 years to more than 12 per cent above 85. The prevalence also increases with age and the problem of dementia will grow over the next twenty years as the life expectancy of our population increases. The strongest predictors of the risk for dementia are age and family history. In *developed countries* where women live longer than men, they have a higher risk of developing dementia simply because their at-risk period is longer. Hypertension, heart disease and hyper-cholesterolemia may increase the risk of dementia perhaps by increasing the risk of stroke which in turn can cause dementia. Head injury and a cholesterol transport protein called apolipoprotein E appear to modify the risk of dementia.

[1] Incidence refers to the number of new cases in a given time period. Prevalence refers to the fraction of the total population that is affected by the disease.

Table 9.16 Causes of dementia

1. Idiopathic, degenerative, abiotrophy	Alzheimer's disease (AD), Pick's disease, frontal lobe dementia, corticobasilar degeneration (discussed in this chapter) Huntington's chorea (HD), Parkinson's disease (PD), Lewy body dementia (LBD), progressive supranuclear palsy (discussed under movement disorders)
2. Vascular dementia	Strokes, Binswanger's disease, amyloid angiopathy, arteritis
3. Alcohol	Wernicke-Korsakoff syndrome; chronic alcoholic dementia
4. Other toxins	Lead, mercury, aluminium
5. Metabolic	Dialysis dementia, recurrent hypoglycemia, hypothyroidism, chronic portosystemic encephalopathy and hepatocerebral degeneration
6. Trauma	Subdural hematoma, diffuse head injury, boxing
7. Hydrocephalus	Obstructive, communicating and normal pressure hydrocephalus (NPH)
8. Malignancy	Primary CNS tumours: gliomas and lymphomas (infiltrate brain parenchyma) and meningioma (exerts pressure effects) Systemic tumours: metastases, meningeal involvement, effects of radiation and chemotherapy, paraneoplastic (limbic encephalitis)
9. Infections	Viral encephalitides e.g., herpes simplex Slow viruses: Creutzfeldt-Jakob disease, progressive multifocal leukoencephalopathy, HIV, SSPE Bacterial: syphilis, tubercular Fungal: cryptococcus Parasitic: cysticercosis
10. Demyelinating diseases	Advanced multiple sclerosis, Schilder's disease
11. Poliodystrophies and lipid storage disorders	
12. Leukodystrophies	

Etiopathogenesis Fifty to sixty per cent of patients with dementia have Alzheimer's disease. Approximately five to thirty per cent have 'vascular' dementia secondary to multiple infarcts. In 10–15% both factors act to together to result in dementia. The various causes of dementia are listed in Table 9.16. Alzheimer's disease, some of the rarer types of degenerative dementia and vascular dementia will be discussed in this section. Other causes will be discussed in other sections such as **Movement disorders, Infections** etc. In younger patients presenting with dementia it is particularly important to rule out infections, tumours, inherited metabolic conditions and treatable causes of dementia. Alzheimer's disease rarely becomes symptomatic below the age of 65 years unless there is a family history of early onset Alzheimer's disease.

Alzheimer's Disease

Alzheimer's diesease was first described by Alois Alzheimer who presented a comprehensive clinicopathological description of the disease in a 55 year old woman, in the year 1907. At that time 'general paresis of the insane' that is, syphilis, was a more prominent cause of dementia. The diagnosis of Alzheimer's disease can only be made with certainty in an autopsy. However, in a patient in the right age group (40–90 years; most likely in age group 65–85 years) who has a steadily progressive dementia with prominent impairment of memory and orientation and in whom no alternative cause for the dementia is found, the clinical diagnosis of Alzheimer's disease can be made with reasonable certainty.

Pathology The areas maximally affected are the hippocampal formation, amygdala, entorhinal cortex (the anterior portion of the parahippocampal gyrus), cerebral cortex (association areas), basal forebrain nuclei and locus the ceruleus. The basal ganglia, thalamus, substantia nigra and cerebellum are relatively unaffected. In the involved areas the changes seen are neuronal loss, gliosis, neurofibrillary tangles and amyloid plaques. Neurofibrillary tangles are basophilic, argyrophilic thick fibre-like strands shaped into loops, coils and tangled masses. Typically, they are within the cytoplasm but they may be extracellular (called ghost tangles). Amyloid plaques, also called senile plaques, consist of a central amyloid core, a surrounding layer of dystrophic neurites (swollen axons and dendrites containing paired helical filaments, abnormal mitochondria and lysosomal dense bodies) and an outermost layer of microglia and reactive astrocytes.

Pathophysiology There is deposition of amyloid in the parenchyma and some neuropathologists suspect that the amyloid is toxic to surrounding neurons. Amyloid is an insoluble protein with certain staining properties.[1] The amyloid in AD contains a beta-amyloid peptide or A4 peptide in a special beta-pleated configuration. There are also deposited in the plaque some circulating proteins such as α_1-antitrypsin and apolipoprotein E whose contribution is unclear. They may serve as 'chaperones' regulating protein folding (tertiary structure). Beta-amyloid represents a transmembrane fragment of beta amyloid precursor protein (b-APP) a constitutive, transmembrane protein which has at least four genetically determined isoforms and is degraded by at least two pathways– a secretory and a lysosomal pathway. Beta-amyloid is detected in normal CSF, so it is not clear why it is deposited in an amyloid form in patients. Some isoforms and degradative pathways are more amyloidogenic.

Other neurologists feel that the amyloid is a byproduct of neuronal degeneration and the cause is related to the tau protein in neuro-

[1] Amyloid stains pink (eosinophilic) in hematoxylin-eosin-it also stains pink (colour change or metachromasia) with crystal violet and shows a unique green birefringence under the polarising microscope with Congo-red staining. Immunohistochemistry is the easiest way to visualise amyloid.

fibrillary tangles. Tau is a neurofilament protein which undergoes abnormal phosphorylation in Alzheimer's disease and is the chief component of paired helical filament within neurofibrillary tangles. In the normal state tau is a protein component of microtubules within neurons. Alz 50 is an antibody that binds to abnormally phosphorylated tau protein and is used to detect tangles in pathological specimens.

A deficiency of NGF (nerve growth factor) has been shown in Alzheimer's disease. There are also multiple neurochemical changes involving more than one neurotransmitter system. Decreased acetylcholine is noted in the septo-hippocampal pathways and cerebral cortex; decreased cortical norepinephrine, serotonin, somatostatin and corticotrophin releasing factor (CRF) have also been described.

The epsilon 4 ($\epsilon 4$) allele of the apolipoprotein E gene (on chromosome 19q13) appears to be an important risk factor[1] for earlier onset and perhaps increased risk of AD; the $\epsilon 2$ allele may be protective. Apolipoprotein E binds to both the beta-amyloid protein and to the tau protein. A commercial test is now available but its use is advised only in 'study' situations.

Cerebral amyloid angiopathy (congophilic angiopathy) is seen with AD more frequently than would be expected by chance but its role in disease pathogenesis is unclear.

Genetics Alzheimer's disease (AD) is described as early onset if symptoms manifest before the age of 65 years and late onset if symptoms begin thereafter. Early onset AD is more often familial and late onset AD is more often sporadic. Early onset AD is associated with an abnormality on chromosome 21 (the amyloid precursor protein gene) in a few families. In many other families with early onset AD, the disease has been linked to a gene on chromosome 14.

[1] The risk for developing Alzheimer's disease is approximately doubled in patients with the apolipoprotein E $\epsilon 4$ allele.

Clinical course

Symptoms: Typically the onset of symptoms is insidious. In some patients a gradual deterioration may be suddenly highlighted by an acute medical illness, death of spouse, moving or retirement. The patient, a friend or relative notices that the patient is having difficulty coping with the usual responsibilities on the job, in handling finances or in cooking and keeping house. The patient may forget about important appointments or become obsessive about writing them down. There may be a decline in the ability to keep track of one's own health problems or medication. Names of old friends and events that occurred only a few days earlier may be forgetten. Later she may forget what has been said even in the course of a simple conversation and therefore, repeat things several times.

The patient may lose her way while travelling or have an accident due to poor judgement while driving. Later on in the course of the disease she may lose her way even in her own street or home. There may be a gradual loss in awareness of year, date, day, month and season. In late stages she may no longer recognise her relatives.

Personality changes occur. She may give up hobbies because they seem difficult, and may appear tactless in social situations. The patient may become apathetic (docile) and clinging or irritable and paranoid imagining that people are trying to hurt her or steal from her. Sexually inappropriate behaviour may occur. In late stages there may be repetitive, meaningless activities such as tearing up pieces of paper and hiding things in inappropriate places. There may be hallucinations and delusions with the patient talking to long-dead relatives or imagining she is in her childhood home.

Failure to thrive occurs in many patients because the patient cannot or will not eat. Initially the patient can look after her own needs such as bathing and dressing but may need help later. The diurnal pattern may be disturbed with daytime napping and nighttime insomnia. Incontinence may be present.

Many of the changes described above may occur as a consequence of normal age-related changes such as retirement, change of financial and social status as children become independent or due to physical disabilities. Hence a diagnosis of dementia should only be made if there is a clear-cut downhill course.

A patient with end-stage Alzheimer's disease is in a persistent vegetative state — mute, immobile and apathetic. Sleep-wake cycles are seen and swallowing may be intact. Decerebrate or decorticate posturing and myoclonus may be seen. The patient may still react to significant environmental changes by decreased food intake or moaning. The terminal event is often an infection — pneumonia or urinary tract infection.

Prognosis The course leads inexorably downhill but the rate of decline varies enormously and many patients die of other causes such as concurrent heart disease. The life-expectancy is usually 5–15 years from the onset of symptoms but may be as short as two years in patients who are diagnosed at a late stage.

Examination of a patient with dementia

All patients presenting with dementia deserve a complete general physical and neurological examination at the time of the first clinical evaluation. If necessary, the patient is admitted or the examination completed over two sessions. General physical examination should include an evaluation of the heart, cerebral vasculature and thyroid function. Anemia or signs of alcoholism suggest a nutritional deficiency. Subcutaneous cysticerci should be sought. The breast cervix, lungs, prostate and lymph nodes should be examined for an occult malignancy.

The neurological examination should include a detailed cognitive assessment as outlined at the beginning of this section. During subsequent visits, repeat evaluation of cognitive status using a standardised format (such as the Folstein mini-mental status examination) permits one to assess how much the patient has declined between visits.

In the examination of cranial nerves, vision and hearing should be specifically assessed as impairment of these functions may spuriously give an impression of dementia. A fundus examination should be done to look for diabetic or hypertensive changes. Eye movement abnormalities suggest progressive supranuclear palsy. A typical patient with Alzheimer's disease will have no abnormality on cranial nerve examination. The presence of cranial nerve palsies should raise a concern of chronic meningitis (either infective or malignant).

In the motor examination patients with Alzheimer's typically show no abnormalities. Sometimes the tone may be mildly increased but typical 'cogwheel' rigidity is rare in early AD. Gait is normal but may be stiff in late AD. A Parkinsonian syndrome suggests Lewy body dementia or a combination of Parkinson's disease and AD. Myoclonus is seen in Creutzfeldt-Jakob disease, uremic encephalopathy and hypoxic encephalopathy but also in the later stages of AD.

Deep tendon reflexes are normal in AD, their absence may suggest a B_{12} deficiency. Upgoing plantars may be seen in late Alzheimer's, but if they are asymmetric a structural lesion may be present. Frontal release reflexes may be positive (grasp, palmomental, suck, snout and glabellar reflexes).

Sensory examination is typically unremarkable; mild vibration loss and a positive Romberg sign may be seen due to ageing-related sensory neuropathy or B_{12} deficiency. Neck stiffness should not occur at any stage of Alzheimer's disease and a lumbar puncture is indicated, if it is present.

Common problems in the differential diagnosis of dementia in the elderly

Healthy adults may worry that their memory is not what it used to be. On cognitive testing such individuals are either normal or show isolated mild memory impairment which does not worsen with time. Depressed individuals may have symptoms suggestive of dementia

(pseudodementia). An experienced neuropsychologist can usually differentiate between the pattern of cognitive deficits in dementia and pseudodementia. If the patient is depressed, the depression is treated and cognitive function retested. Some patients may have impaired cognition as a side effect of the medication they are taking (for example, patients on a sedative.) Two eminently treatable causes of dementia that should not be missed are chronic meningitis and a subdural hematoma. A subdural hematoma may be chronic and bilateral; the trauma which caused it may have been occult, making the diagnosis difficult unless there is a high index of suspicion. A careful examination does usually reveal some focal sign, perhaps only an extensor plantar response.

Another problem is differentiating between dementia and an acute confusional state. *Confusion* is a general term denoting an incapacity of the patient to think with customary speed, clarity or coherence. The most conspicuous attributes are *disorientation, impaired attention* and concentration, impaired registration and recall and a diminished capacity for all mental activity. Confusion may be seen chronically in moderate dementia. An acute confusional state is usually due to a systemic problem and is commonly seen in a postsurgical setting, in metabolic encephalopathies (uremia, hypoxia including pulmonary thromboembolism and pneumonia, hepatic failure, dyselectrolytemia), with infections (meningitis, encephalitis, pneumonia, septicemia) and intoxication (drugs, alcohol). Delirium is a special type of acute confusional state with a prominent disorder of perception (hallucinations), hypervigilance, sleep disturbance, emotional disturbances, autonomic and psychomotor hyperactivity and sometimes seizures (for example, delirium tremens). This is discussed in the chapter on psychiatry. Beclouded dementia is the term used for delirium superimposed on mild dementia.

Investigations A hemogram and serum biochemistry are done to assess blood sugar, electrolytes, liver and renal function. Serum B_{12} and thyroid function tests (TSH, T4) are also indicated. An ESR (raised in temporal arteritis and aortoarteritis), serological test for syphilis, carotid Doppler, electrocardiogram and chest X-ray may be performed if *the history indicates a need for them.* An imaging study is often done to rule out an intracranial hematoma, stroke, tumour or hydrocephalus. A CT scan of the head (without contrast) is sufficient in most patients. An MRI of the head is more likely to pick up small infarcts but the significance of asymptomatic white matter hyperintensities picked up on the MRI is unclear. In most patients there is no advantage in obtaining a more expensive test such as an MRI. In research settings however, an MRI can detect the hippocampal atrophy seen in Alzheimer's disease. An EEG may be done if Creutzfeldt-Jakob disease is suspected or if there are episodic cognitive or behavioural problems suggesting partial complex seizures. SPECT and PET have been used in research settings to resolve diagnostic problems in patients with an atypical presentation of dementia. The pattern of decreased bloodflow is symmetrical and parietotemporal in Alzheimer's disease, symmetrically frontotemporal in Pick's disease (discussed later in this chapter) and, asymmetrical and multifocal in vascular dementia. The clinical value of these tests is still unclear. In centres where qualified neuropsychologists are available, neuropsychological testing can confirm the diagnosis in patients with mild disease, help define the type and degree of dementia, detect associated depression, and define the areas of retained cognitive ability thus aiding in management.

Management Although Alzheimer's disease is currently incurable, *it is not untreatable.* It is important for the doctor concerned to remain available to help the patient and family through different stages of the illness. In the early stages it is important to treat the patient with respect

and involve her in decisions. The person caring for a patient with dementia bears a large 'caregiver burden' and should be treated with understanding and support. Education about what to expect and how others cope is very useful.

Drug treatments for AD are still in the investigational stage. Tacrine, an anticholinesterase inhibitor with marginal benefit, has been approved by the FDA, and is widely used in the United States not because it is very useful but simply due to the lack of an alternative agent. It is started as 10 mg qid and gradually increased to a 40 mg qid dose. Side effects are caused by increased concentrations of acetylcholine outside the brain and include nausea, vomiting, diarrhea and abdominal cramps. Regular liver function tests are required as hepatotoxicity may occur. Many drugs tested earlier have been found ineffective– hydergine, lecithin, nootropics, chelators and vasodilators. For the management of behavioural problems the caregiver is taught to keep the environment safe, safeguard valuables, avoid confrontation if the issue is not important (for example, disorientation regarding the date or addressing a friend by a wrong name). If the patient tends to wander and get lost, a latch on the gate which is too complex for her to open and an ID bracelet are useful. Sometimes patients require medication to control aggressive behavior or distressing hallucinations. Haloperidol in a very small dose (0.5 mg once or twice a day) is often effective in controlling the behaviour problem but may further worsen the patient's cognitive function.

Other Non-Alzheimer Dementias

Pick's disease

This a degenerative dementia characterised by marked frontotemporal atrophy involving both grey and white matter, that is, the atrophy is lobar rather than diffuse cortical atrophy. The clinical picture is correspondingly more frontotemporal. The symptoms may be predominantly 'frontal' affecting initiative, judgement and social behaviour or the patient may present with mainly aphasia. Lobar atrophy is seen on CT or MRI. At autopsy the distinguishing feature is the presence of swollen, 'ballooned' neurons containing cytoplasmic Pick bodies. Pick bodies are argentophilic (silver-staining), are made up of straight fibrils (unlike the neurofibrillary tangle) and are most numerous in the hippocampi.

Subcortical dementias

The type of dementia sometimes seen in pure Parkinson's disease and always seen in Huntington's disease has been called *subcortical dementia* as contrasted with the cortical dementia of Alzheimer's disease. The speed of response is effected more than the ultimate accuracy of response. The problem appears to be one of slowed 'access' rather than an inability to store memories. Some types of vascular dementia may present in this way.

Prion disease

(Proteinaceous infectious particle): Creutzfeldt-Jakob disease is suspected in dementia with a younger age at onset and more rapid decline, than AD. It is discussed under 'Slow Virus Diseases'. Myoclonus is common and the patient may show seizures, blindness and early behavioural changes. Other prion diseases also showing dementia are Gerstmann-Straussler-Scheinker syndrome (dementia and ataxia with myoclonus), Kuru and fatal familial insomnia (dementia and autonomic disturbances).

Lewy body dementia (LBD)

This condition is defined pathologically by the presence of Lewy bodies in the substantia nigra and extensively in the cerebral cortex.

Some patients have no associated neuropathological changes suggestive of AD. Others do show AD changes (plaques and tangles) and are said to represent a Lewy body variant of AD. The two conditions may be part of a continuum. It is uncertain if patients with Lewy body

dementia can be clinically distinguished from those with AD. Suggestive features are an early onset of psychosis and motor symptoms suggestive of a Parkinsonian syndrome (often without tremor).

Static dementia

This is seen after a single, severe injury such as a head injury, encephalitis or cardiac arrest. If delayed deterioration occurs one should look for a cause such as the development of hydrocephalus.

Atypical/incomplete dementia

In some patients a single cognitive function is predominantly or exclusively affected. Gradual clinical deterioration may be associated with progressive focal atrophy of one area on imaging. Pathologically this syndrome is a 'mixed bag' and many patients have Alzheimer's disease. A common example is primary progressive aphasia where language function is almost exclusively lost. Brain tumours should be excluded.

Cortico-basal ganglionic degeneration

This rare disease begins asymmetrically with unilateral extrapyramidal features (rigidity, bradykinesia and tremor) and apraxia. Voluntary efforts to move the limb may result in bizarre movements of the same or contralateral limb (alien hand syndrome). Later the disease becomes bilateral and symptoms may include dementia, distal muscle wasting, proprioceptive impairment and myoclonus. Pathologically there is cortical atrophy (prefrontal, frontal and sometimes anterior parietal) along with degeneration of the substantia nigra. The neurons are swollen and stain lightly (neuronal achromasia).

Fig 9.19 Dementia in AIDS

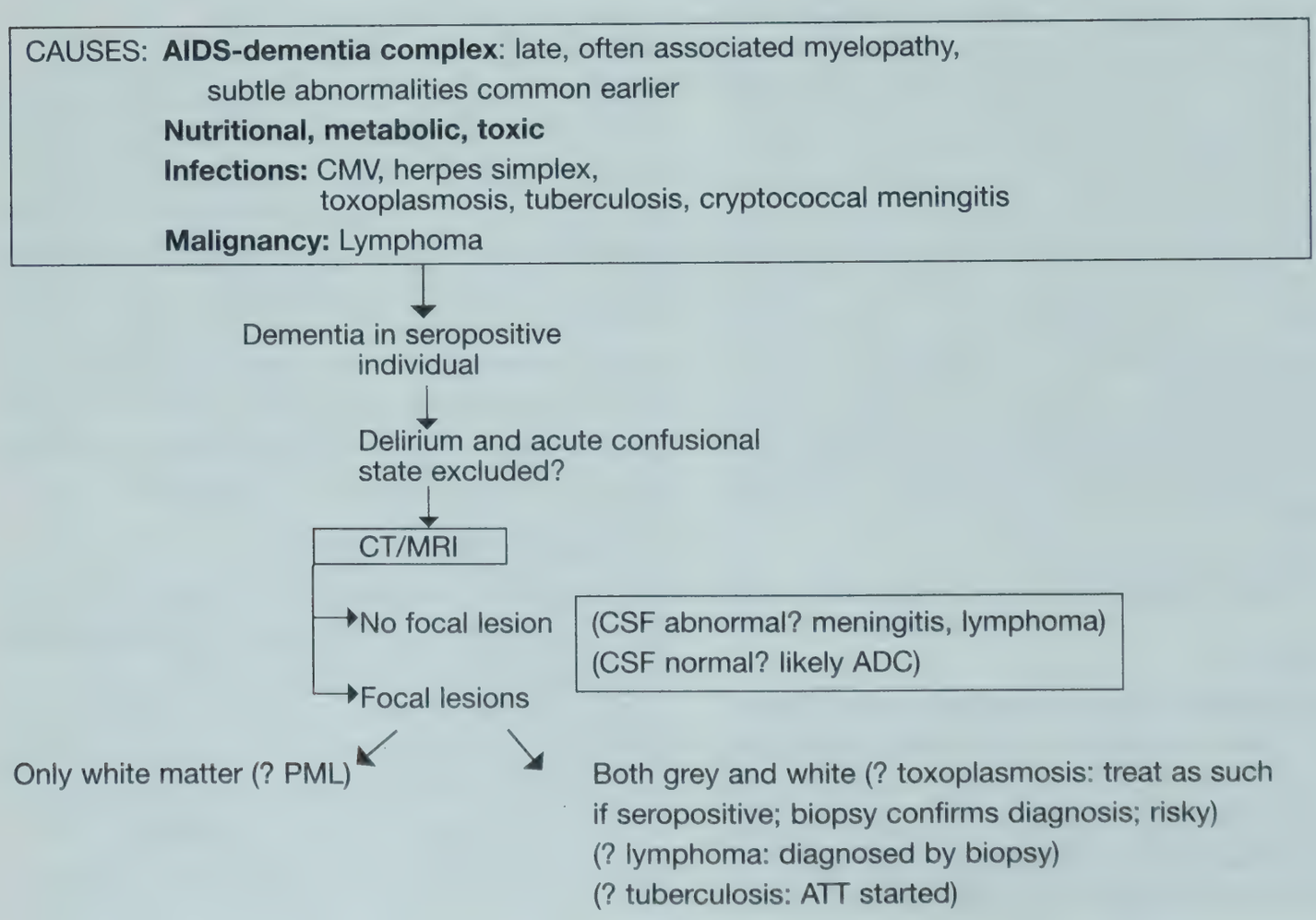


Table 9.17 Reversible dementias: a few important causes

Etiology	*Clinical features*	*Investigations*	*Management*
Normal pressure hydrocephalus	triad of gait disorder, psychomotor slowing and urinary incontinence	CT, MRI, radionuclide cisternogram, Infusion studies: Trial taps	therapeutic shunting: (VA, VP-low pressure valve in shunt)
B_{12} deficiency: Causes are nutritional and pernicious anemia	peripheral paresthesia, abnormal gait, anemia, centrocecal scotoma, impaired vibration sense (posterior column), upgoing plantar (corticospinal tract)	serum B_{12} levels are below 200 pg/ml, usually below 100 pg/ml	parenteral B_{12} 1000 μg im daily for 1 week, weekly for 1 month, then monthly; sometimes oral B_{12} will suffice
Depression	maximal impairment in attention, orientation is OK; may point out rather than hide errors; lifestyle more affected than cognitive capacity would suggest; patient may be tearful, even suicidal	typically do well on formal cognitive testing; endorse symptoms of depression	
Syphilis: Onset 15 to 20 years after initial infection if that is never treated; may be secondary to congenital infection	dysarthria, tremors, hyperreflexia, Babinski, Argyll Robertson pupil, myoclonus, seizures	CSF pleocytosis; FTA-ABS and TPI positive	penicillin G 4 million units iv q 4 hours for 14 days

VA = ventriculoatrial, VP = ventriculoperitoneal

Limbic encephalitis

This is a paraneoplastic syndrome which occurs in patients with lung cancer (small-cell cancer). The clinical presentation consists of personality changes (agitation), memory impairment, and seizures. The CSF shows mild lymphocytic pleocytosis. The EEG shows slowing of activity with intermittent sharp waves localisable to the medial portion of the temporal lobes or the frontal lobes. Pathological changes resemble those of viral encephalitis; hence, a viral etiology has been suspected but not proved. Changes are most marked in the hippocampus and amygdala. Brainstem encephalitis can also occur as a paraneoplastic syndrome. The illness evolves over weeks, is rapidly progressive and leads to death within an year.

KEY CONCEPTS

Alzheimer's disease

- ➢ This disorder is characterised by a progressive decline in intellectual function resulting in the reduced ability to perform activities of daily living. Histopathologic findings are characteristic: there is a loss of neurons in the hippocampus, basal forebrain, cerebral cortex along with the presence of senile *amyloid plaques* and *neurofibrillary tangles*.
- ➢ Alzheimer's disease accounts for over 50 per cent of all dementias. The incidence of the disease increases with age. There is an association with the apolipoprotein ε_4 allele on chromosome 19. Familial forms are linked to chromosomes 1, 14 and 21.
- ➢ Illness begins with a loss of memory for recent events and an impairment of judgement and insight. Soon there is difficulty with daily activities. The patient may wander and get lost. Apraxia, fluent aphasia, remote memory-loss set in and the patient may become bedridden.
- ➢ Diagnosis is clinical. It is important to exclude depression and treatable causes of dementia (notably chronic subdural hematoma, chronic meningitis, B_{12} deficiency, hypothyroidism). A CT scan reveals diffuse atrophy, wide sulci, and dilated ventricles. *Multiinfarct* dementia can be distinguished on a CT scan.
- ➢ Treatment is supportive; counselling of family and caregivers, involvement in support groups, and provision of home care aids are important adjunctive measures.

Pick's disease

- ➢ This is a rare cause of dementia with histological evidence of circumscribed atrophy of the frontal and temporal cortices.
- ➢ Personality changes are prominent and may antedate intellectual impairment.
- ➢ A CT scan shows frontotemporal atrophy. The pathologic hallmark is the presence of *Pick bodies*.

9.7 Movement disorders

The basal ganglia

The structures conventionally included as part of the extrapyramidal system are the basal ganglia (caudate nucleus and lentiform nucleus), the subthalamic nucleus of Luys in the diencephalon, the substantia nigra and the red nucleus[1] in the midbrain. The lentiform nucleus (so called because of its shape) lies lateral to the internal capsule and is divided into an outer putamen and an inner globus pallidus. Functionally, the caudate nucleus which lies in the medial wall of the lateral ventricle shares a greater degree of structural and functional similarity with the putamen than the globus pallidus. Hence, the caudate and putamen are grouped together as the *striatum*.

Ultrastructurally, the various nuclei contain small cells which receive and integrate afferent input and send impulses to adjacent large-celled neurons. These large-celled neurons generate the efferent output. The small striatal neurons receive afferents from the cerebral cortex (*corticostriate*), the ventral anterior nucleus of the thalamus (*thalamostriate*), and the large-celled 'pars compacta' portion of the substantia nigra (*nigrostriatal pathway*). The striatum in turn projects to the globus pallidus which sends efferent fibres to the ventral anterior and ventrolateral thalamic nuclei (*pallido-thalamic*) and to the subthalamus. A few large cells within the striatum project to the small-celled portion (*pars reticulata*) of the substantia nigra (*striatonigral pathway*). The basal ganglia project to the cortex only through the thalamus. If one of the inputs to the striatal integrating system is either excessive or insufficient, the output by way of the globus pallidus and thalamus to the cerebral cortex is altered and movement disorders result.

The neurotransmitters involved in these various pathways are numerous. The corticostriate pathways release glutamate, and dopamine is the transmitter for the nigrostrial pathway. Within the striatum, acetylcholine and substance P appear to be excitatory neurotransmitters while GABA (γ-amino butyric acid) is the chief inhibitory neurotransmitter. The dopaminergic nigrostriatal pathway has an inhibitory effect on the striatum. Hence, decrease in dopamine activity and increase of acetylcholine activity within the striatum have similar effects. This is why in Parkinson's disease there are two classes of drugs: the anticholinergic agents and the dopaminergic agents.

MOVEMENT DISORDERS

Movement disorders are defined as neurological disorders characterised by either presence of abnormal involuntary movements (*hyperkinesias*) or slowness and paucity of desired movements (*hypokinesia*). They are not associated with either weakness or spasticity. Most movement disorders are due to

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[1] The red nucleus receives afferents from the cerebellum and projects to the spinal cord. It is functionally more closely related to the cerebellum than to the basal ganglia.

dysfunction of the basal ganglia. The classic hypokinetic syndrome is Parkinson's disease. There are a variety of hyperkinesias including tremors, dystonias, chorea, athetosis, ballismus, tics, myoclonus and akathisia.

Parkinson's Disease (Paralysis Agitans)

Parkinson's disease is a slowly progressive nervous system disorder chiefly affecting the extrapyramidal system, affecting mature adults and has a characteristic clinical picture.

Epidemiology Parkinson's disease is prevalent in about 1 per cent of the adult population over the age of 50 years. The age of onset ranges between 30–70 years with an average onset age of 55 years. The male-female ratio is 3:2.

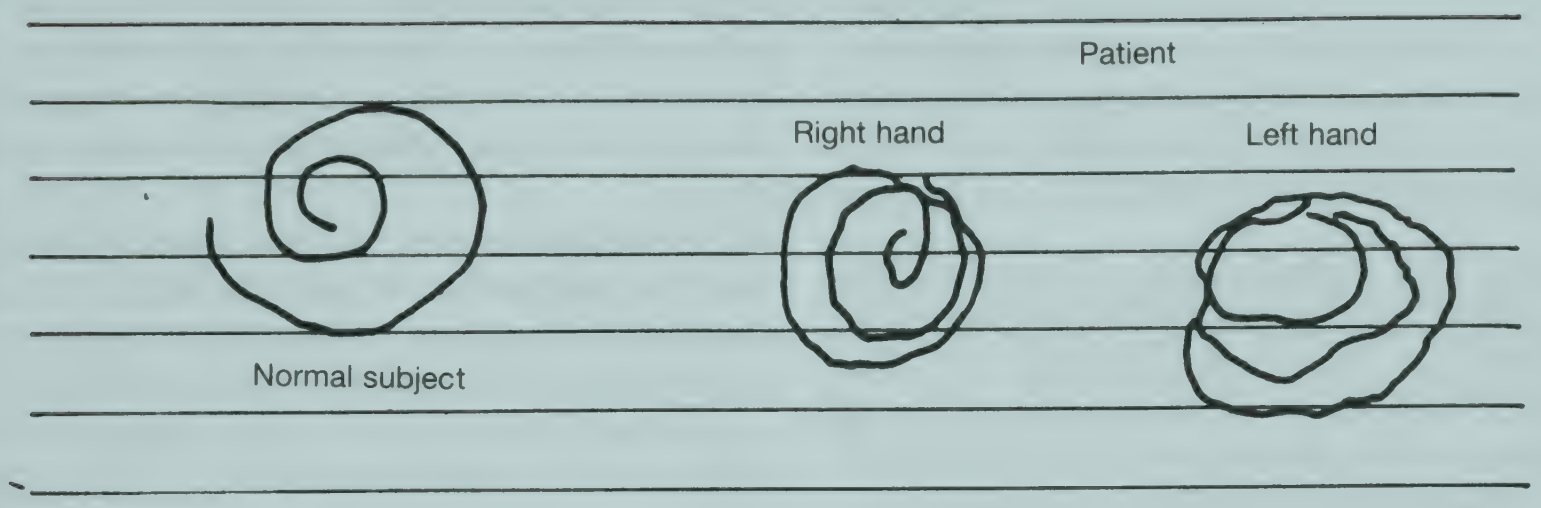
Clinical findings The classical description of the disease by James Parkinson in 1817 contains almost all the major manifestations of the disease. The patient looks abnormal: the face is expressionless (*mask-like facies*) and the frequency of eye-blinking is decreased;[1] the eyes appear to be staring ahead. The patient appears to move stiffly and slowly as he sits, stands up or begins to walk. This slowness and difficulty in the initiation of voluntary (willed) movements is called *bradykinesia*. There is also a poverty of movement (*hypokinesia*) — the patient makes fewer spontaneous gestures while talking, listening, or walking. When the patient stands erect there is mild flexion of the head and trunk, elbows and knees. The feet may be placed slightly apart. There is postural instability so that the patient may need to take a step to prevent falling if given a firm but gentle forward or backward push on the sternum while standing.[2] The walk is described as a 'Parkinsonian or *festinant gait*.' While walking the patient leans forward and starts walking very slowly with a shuffling gait and short steps. After a few steps the patient moves forward faster and faster, as though to catch up with his own centre of gravity. There is a decrease of associated arm movement. A small obstacle such as a threshold may stop the patient in his tracks. The act of turning around is achieved by bringing both feet together and then moving around in a series of small steps (turn en bloc) rather than in the smooth fashion typical of a normal person.

There is a *resting tremor* characteristically involving the hands in a '*pill-rolling*' movement. The tremor diminishes during voluntary movement and disappears during sleep. It is increased by emotional stress. If the patient is asked to draw a spiral the tremor is clearly brought out in the picture (Fig 9.20). The handwriting becomes small and cramped particularly towards the end of a sentence (micrographia). Rigidity is a type of hypertonia caused by a uniform increase in muscle tone in all limb muscles (unlike spasticity where tone is selectively increased to a greater extent in some muscle groups). Also unlike spasticity, power and reflexes remain nearly normal. The rigidity may remain normal throughout the range of movements imposed by the examiner ('*lead-pipe' rigidity*, also called plastic rigidity or *gegenhalten*) or it may be interrupted by a regular series of brief interruptions similar to the sensation of moving a lever over a cogged gear wheel (*cog-wheel* rigidity). In Parkinson's disease cog-wheel rigidity is seen, lead-pipe rigidity being more common with frontal lobe lesions. The patient complains not of 'rigidity' but of muscle pain, fatigue and joint stiffness. At the outset, all symptoms are typically asymmetrical with one side being affected more than the other. Later the symptoms are bilateral.

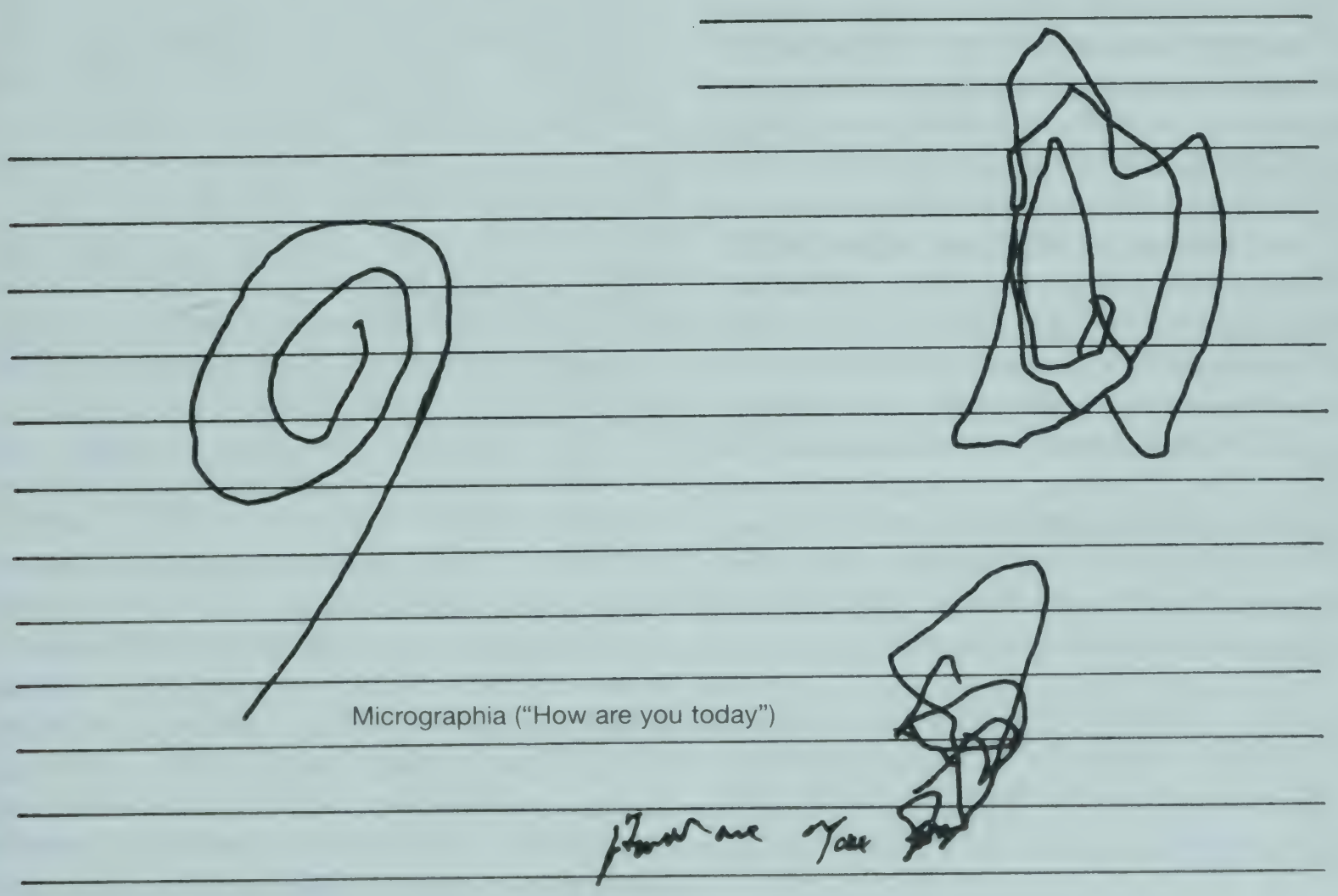
Other symptoms include seborrhea and increased salivation, postural hypotension, depression and in rare cases, dementia. The dementia is characterised by prominent bradyphrenia (slowness of responses to

[1] The usual rate of blinking is about twenty per minute; in Parkinson's disease this is reduced to 5–10 per minute.

[2] In this situation the tendency to fall forward is called propulsion and the tendency to fall backwards is called retropulsion.



a. A patient with mild Parkinson's disease



b. A patient with severe Parkinsonism

Fig 9.20 Spiral drawing and micrographia in Parkinson's disease

questions). Sleep disturbances may include an inability to turn in bed as well as the occurrence of nightmares. Daytime hallucinations may occur due to the disease or as a side effect of the treatment (dopamine-induced).

Pathology and pathogenesis There are two pathological features that are characteristic of the brain in Parkinson's disease. 1) The substantia nigra shows neuronal loss, surviving neurons show *depigmentation* and there may be extracellular pigment. 2) The substantia nigra neurons also show characteristic inclusions called *Lewy bodies*. These are eosinophilic, rounded and occur in the cytoplasm, (typically one per cell and surrounded by a clear area — halo). They are made up of neurofilaments and a protein called *ubiquitin* whose function is to help remove degenerating intracellular components.

Associated with the loss of nigral neurons there is a degeneration of the dopaminergic nigrostriatal pathway and hence a deficiency of dopamine in the putamen.[1] Genetic susceptibility as well as environmental factors probably play a role in the development of Parkinson's disease. A substance called MPTP (methyl phenyl tetrahydropyridine, a pethidine analogue used by heroin addicts in California) resulted in a cluster of young-onset Parkinson's disease. Giving this substance to monkeys induces a Parkinsonian syndrome in them. The toxicity of this substance is reduced by drugs which inhibit the enzyme monoamine oxidase type B. MPTP is rare and cannot account for most cases of Parkinson's disease but has given us insights into the pathogenesis of this disease.

Treatment Parkinson's disease is one of the few neurological diseases for which remarkably effective treatments are available. We are just beginning to explore ways of slowing down the underlying disease process but we do have a drug that produces an almost miraculous improvement in symptoms, in over 85 per cent of patients. This drug is levodopa, a precursor of dopamine. Unfortunately, the drug becomes less effective with progression of the underlying disease.

A. *Altering the course of the disease*: A drug called seligeline or deprenyl, which is an inhibitor of the enzyme monoamine oxidase type B, may be effective in slowing the rate of disease progression. Since deprenyl also provides some symptomatic improvement by reducing breakdown of dopamine in the striatum it is a useful drug for very early Parkinson's disease at a dosage of 5 mg given once daily or twice daily at 8 a.m. and 2 p.m. A late evening dose may cause insomnia.

B. *Symptomatic treatment*: When the patient is distressed or disabled by his symptoms, for example, if it affects work, it is time to start levodopa. Dopamine is the substance known to be reduced in the brain of patients with Parkinson's disease. Dopamine administered orally will not, however, enter the brain. Hence, the precursor, levodopa, a neutral amino acid is administered. It is absorbed in the small intestine, readily crosses the blood-brain barrier and is converted by an endogenous enzyme, (dopadecarboxylase) to active dopamine. When this conversion occurs outside the brain there are side effects of nausea, vomiting and hypotension and less drug left to enter the brain. Hence, levodopa is administered along with an inhibitor of the dopadecarboxylase enzyme which will act systemically but will not cross the blood-brain barrier to inhibit dopa-decarboxylase in the brain. The enzyme inhibitor used is 'carbidopa'. Two combinations of levodopa-carbidopa are available, a 100 mg/25 mg combination and a 250 mg/25 mg combination. The former is useful in the early stages when patients require smaller doses; later the 250/25 combination is more economical. Doses required vary from 200 to 1250 mg of levodopa daily. The principles of using levodopa-carbidopa are:

[1] PET scan with ^{18}F-fluorodopa shows decreased dopa uptake in the affected striatum.

1. to start at a low dose and increase gradually as the side effects of nausea and vomiting improve with time;
2. to use the lowest dose that provides adequate relief of symptoms;
3. to adjust the timing of the doses based on the patient's symptoms. The maximal effect is seen half to one hour after a dose and the effect lasts for 3–4 hours, and sometimes longer; and
4. sustained release preparations are more expensive but may be used for special situations. Thus, a patient with severe bradykinesia on awakening may benefit from a sustained release pill given at night.

Side effects of levodopa include hypotension, cardiac arrhythmias, dyspepsia and hallucinations. Giving the drug with meals may reduce dyspepsia but may also make absorption more erratic. An antiemetic such as metoclopramide can reduce the efficacy of levodopa. Levodopa is effective in relieving bradykinesia and rigidity but less effective in reducing tremor.

A variety of anticholinergic agents are available to treat the tremor of Parkinson's disease and these will also reduce the excessive salivation. A commonly used agent is trihexaphenidyl. Amantadine at a dosage of 100 mg b.i.d may be useful in mild Parkinson's disease, relieving both tremor and bradykinesia. Side effects are pedal edema and a mottled rash over the shins called *livedo reticularis.*

Late-stage Parkinson's disease

In 5 to 8 years most patients start showing a diminished benefit from levodopa and show troublesome side effects as well as new symptoms not responsive to therapy. The side effects include involuntary movements (dyskinesias) and involuntary sustained posturing (dystonia). The duration of benefit from each dose shrinks to 1–2 hours and unpredictable attacks of freezing may occur. Dysarthria and dysphagia may occur. If frequent small doses of levodopa do not improve matters, alternatives such as dopamine agonists[1] – bromocriptine (1.25 to 2.5 mg b.i.d) and pergolide (0.05 mg b.i.d) which directly activate the dopaminergic receptors, should be tried. Two previously used surgical approaches, thalamotomy for tremors and pallidotomy for bradykinesia, are rarely used these days. Surgical transplantation of the patient's own adrenal medulla (.a source of dopamine) or fetal substantia nigra is being investigated as a therapeutic option.

Parkinsonism 'plus' Syndromes

When a patient presents with what appears to be Parkinson's disease but has some unusual clinical features, or fails to show any therapeutic response to levodopa, the following diseases should be considered.

1. Parkinsonian features (except for the absence of tremors) with a history of frequent falls, a stiff extended neck, hypophonia and supranuclear gaze palsies suggest **progressive supranuclear palsy.** The eye signs must be present to make the diagnosis. There is an initial loss of vertical eye movements, and later, horizontal movements are affected so that the eyeballs appear frozen in the head and the patient has to turn the head to view anything to one side. The earliest signs are slow saccadic eye movements and loss of the fast component of optokinetic nystagmus.[2] This syndrome, also called the Steele-Richardson-Olzewski syndrome, has a pathological appearance very different from Parkinson's disease. Instead of Lewy bodies, there are neurofibrillary tangles as seen in AD. The biochemical structure of these tangles is different from those in AD; they consist of straight rather than paired helical filaments. There are no amyloid plaques (these are present in AD). Furthermore, the distribution of the tangles is different. The cortex and hippocampus

[1] In patients with early Parkinson's disease who have marked side effects with levodopa, dopamine agonists may be used, either alone or as levodopa-sparing agents.

[2] For a discussion of optokinetic nystagmus see the section on cranial nerves.

have very few tangles, the basal ganglia have a moderate amount and the subthalamus, midbrain and pontine nuclei are full of tangles. This disease occurs in the same age group as Parkinson's disease and patients may show some dementia.

2. **Striatonigral degeneration** closely resembles Parkinson's disease clinically. Two clinical clues that might suggest this diagnosis are the presence of orthostatic hypotension and cerebellar signs. Again the pathology is different from Parkinson's disease; there are no Lewy bodies but neurons are lost from the caudate, putamen, substantia nigra, inferior olives and sympathetic neurons in the spinal cord. Treatment is mainly directed towards the orthostatic hypotension.

3. **Post-encephalitic Parkinsonism** is extremely rare these days. Between 1917–1927 there was an epidemic of encephalitis (van Economo's disease). Several years later subjects presented with Parkinsonian features. A unique symptom was *oculogyric crisis* where the eyeballs would roll up and remain in this position for hours resisting voluntary efforts to move them. Other clinical features not seen in typical Parkinson's disease included disorders of sleep, respiration, behaviour and involuntary movements such as dystonia. Inflammation and neuronal loss in the basal ganglia and midbrain were observed at autopsy.

4. **Parkinson-dementia-amyotrophic lateral sclerosis-complex of Guam** is seen in some Pacific islands (notably the island of Guam). The incidence of a Parkinson-like disease is unusually high. Many patients go on to develop dementia and amyotrophy. This syndrome complex has now become less common. It is thought to be related to ingestion of large amounts of a locally grown cycad nut.

5. An akinetic-rigid (Parkinsonian) syndrome below the age of 21, should raise a suspicion of **Wilson's disease.** Other causes include Hallervorden-Spatz disease (iron deposition in the basal ganglia) and Lesch-Nyhan syndrome.

Tremor

A tremor is an involuntary rhythmic oscillation of a body part. It results from the alternating contraction of opposing muscle groups. It is classified based on its frequency (of oscillation), amplitude of excursion, the aggravating and relieving factors.

The resting tremor of Parkinson's disease and the intention tremor of cerebellar disorders are described under these respective sections. Tremor which is noticed when the patient maintains a posture, such as holding out his hands in front with the fingers extended, is called *postural tremor*. The commonest types are physiological tremor and essential tremor. *Physiological tremor* is usually not visible but may become manifest when a subject is tired, has ingested a lot of caffeine or due to beta 2-adrenergic drugs such as the bronchodilator, salbutamol. Other factors which can exacerbate a physiological tremor are fever, thyrotoxicosis, hypoglycemia, pheochromocytoma and tricyclic antidepressants. The fine physiological tremor has a frequency of 8–11 Hz (oscillations per second).

Essential tremor is an autosomal dominant inherited disorder, the prevalence of which may be as high as 0.5 per cent. Unlike physiological tremor the amplitude of excursion is greater and the frequency usually lower, although it may range from 4–12 Hz. The tremor involves the hands and the patient may have difficulty with writing or may spill drinks. In other patients there is no disability beyond a social embarrassment. Tremor of the head (titubation) or voice may also be seen. Modest doses of alcohol may transiently relieve the symptoms. A more practical approach is the use of propranolol at a dosage of 40 mg to 240 mg per day. Primidone (an anticonvulsant) may also be effective but is more toxic.

Midbrain or *rubral tremor* is a high amplitude, coarse postural tremor which may be present at rest (like a Parkinsonian tremor) and may worsen with voluntary activity (like a cerebellar

tremor). It is rare and is associated with Wilson's disease, multiple sclerosis and structural midbrain lesions.

A tremor can be documented using a special type of EMG called a tremorogram. Simultaneous recordings are made of the muscle contractions in the two opposing muscle groups involved. The exact frequency can be measured and response to therapy objectively documented. In most patients this is not required.

Dystonias

A dystonia may be defined as an involuntary, sustained or spasmodic and repetitive abnormal posturing. Dystonia may be truncal or appendicular, and focal (involving one group of muscles) or generalised. Dystonia may be a symptom of a metabolic or neurological lesion (such as Wilson's disease) or idiopathic. The thalamocortical output appears to be abnormal in dystonia but a variety of basal ganglia lesions can affect this thalamocortical output.

Meige syndrome — craniocervical dystonia[1]

Typically this affects elderly patients. The muscles affected are the orbicularis oculi, orbicularis oris, platysma and the sternocleidomastoid. Other muscles of the face and neck and the tongue may also be involved. The symptoms typically begin with forceful eyelid closure (blepharospasm). This is initially precipitated by fatigue or bright light. Spasms gradually increase in frequency and duration. During the spasms the patient is functionally blind and hence the syndrome is potentially dangerous. Affected patients cannot drive and some cannot even walk. If the symptoms remain restricted to the eyes it is called **idiopathic blepharospasm.** Other patients develop dystonic movements of the face (pouting, grimacing, tongue protrusion, involuntary jaw-opening and jaw-closure) which are socially disabling and may interfere with speech and eating. Neck movements manifest typically as torticollis (head tilted to one side) due to spasm of the sternocleidomastoid.

Medication tried includes anticholinergics (trihexyphenidyl, tricyclic antidepressants), carbamazepine and benzodiazepines (clonazepam). The benefit is marginal. The best available treatment is injection of small doses of botulinum toxin type A (Botox) into the affected muscles. Basically this potent toxin of the neuromuscular junction partially paralyses adjacent muscles. The doses used are too small to cause generalised botulinism. This procedure is standardised for the treatment of blepharospasm and torticollis but is still being perfected in the other focal dystonias. It is a highly specialised technique and should only be performed by trained neurologists who will sometimes use EMG guidance to see which muscles are involved. Unintended paralysis of adjacent musculature can cause side effects of ptosis, diplopia (following injection for blepharospasm) and dysphagia (following treatment for torticollis) and the injection itself can cause a hematoma. Unfortunately, the benefit is transient, lasting only for 8 to 16 weeks. The injections can be repeated but are very expensive and some patients stop responding due to the development of antibodies to the toxins.

Dystonia musculorum deformans

This is a childhood onset, autosomal dominant, generalised dystonia common among Ashkenazi Jews (Jews ethnically from eastern Europe). A gene on chromosome 9q33 has been linked to the disease. A similar syndrome may be seen in other populations and even without a family history (idiopathic torsion dystonia). Onset of symptoms is in adolescence. Initially, there are spasms of dystonia, and later the dystonia is provoked by postural stress such as holding out one's arms or trying to walk. Later, the dystonia is present even at rest and finally, due to prolonged dystonia, secondary contractures develop. The gait in dystonia has been described

[1] A Dutch artist Peter Brughel has painted this syndrome in the sixteenth century.

as a 'dromedary gait'. (A dromedary is a camel with one hump.) Patients may develop spinal curvature (hyperlordosis) and walk slowly and deliberately with a high step and on their toes since the muscle spasms render rapid movement impossible. Dystonic spasms can be painful. Unless bulbar spasms supervene, the disease is disabling but not life-threatening. A few patients respond to levodopa **(dopa responsive dystonia)**. Most patients do not respond to any medication.

Hemifacial spasm

A fairly common focal dystonia or perhaps a tic, it presents with painless hemifacial spasms. Younger patients usually complain of social embarrassment. Treatment procedures are similar to those for blepharospasm.

Writer's cramp

This is focal dystonia which is induced only by a specific activity. Thus the patient's hand goes into spasm whenever he grips a pen but he may be able to use a fork without difficulty. Variants include musician's cramp. Initially a psychogenic etiology was suspected but there does seem to be an organic component in most patients. Again, the management is as for blepharospasm. In addition the patient may start writing with the other hand (which often becomes affected once it is used for writing!) or use other modalities such as typing.

Drug-Induced Acute Dystonic Reactions

This is typically seen in younger patients who have been prescribed metoclopramide for nausea or vomiting and present in the emergency room with hyperextension of the neck and oculogyric crisis (eyeballs rolled upwards or laterally). There may be torticollis, athetosis and opisthotonic posturing (arching of back). The withdrawal of the offending agent results in gradual resolution of symptoms. Oral diphenylhydramine (Benadryl) or parenteral promethazine (Phenergan) may shorten the duration of symptoms.

Choreoathetosis

Chorea consists of irregular, unpredictable, brief, jerky, semipurposive movements that flit from one body part to another. Besides the various conditions discussed below, rarer causes of chorea include thyrotoxicosis, systemic lupus erythematosus, polycythemia, pregnancy **(chorea gravidarum)** and oral contraceptives. Chorea is characteristically associated with a structural or autoimmune lesion in the contralateral caudate. The biochemical basis may be increased dopaminergic activity since dopamine depleting drugs (haloperidol) alleviate symptoms.

The term **athetosis** describes limb movements that are slow, sinuous and writhing. Isolated athetosis is rare but may be seen in cerebral palsy, cerebral anoxia and Wilson's disease. Athetosis is combined with chorea in Huntington's disease.

Sydenham's chorea or rheumatic chorea is discussed in the chapter on rheumatic fever.

PKCA

Paroxysmal kinesogenic choreoathetosis is an autosomal dominant inherited disorder characterised by numerous brief attacks of choreoathetosis, sometimes involving only one limb, and provoked by any sudden movement. Patients are young adults. The condition may be mistaken for partial seizures. The response to antiepileptic drugs (phenytoin) is excellent.

Neuroacanthocytosis

This is an autosomal recessive inherited disorder which usually presents in the third or fourth decade of life. There is generalised chorea. In addition there is a unique clinical picture of uncontrollable lip and tongue biting (self-mutilation), spasms of the tongue which may interfere with speech (lingual dystonia) and involuntary vocalisations (grunts, cries, sighs). Eating may provoke such bizarre oral movements (including spitting), that the patient may not like to eat in company. There may be

seizures, peripheral wasting and absent reflexes. On testing, the diagnosis is established if a peripheral blood smear shows at least 15 per cent acanthocytes. A CT or an MRI shows caudate atrophy; serum creatine phosphokinase levels are elevated. The disorder is rare but has been described in India. The genetic and biochemical basis of the illness are as yet unknown. There is no effective therapy.

Huntington's disease

Huntington's chorea is a disease characterised by autosomal dominant inheritance, choreo-athetosis and dementia with a major component of behavioural abnormalities.

Epidemiology Huntington's chorea has been described in all parts of the world but its frequency varies. The average prevalence is 1 per 200,000. The disease typically begins in the fourth or fifth decade of life. In successive generations the disease onset may begin earlier, a phenomenon which is called *anticipation.*

Clinical features The mental disorder often begins with behavioural changes such as irritability, paranoia, and outbursts of temper. Gradually the patient becomes withdrawn and slow in his thinking. This pattern wherein the speed of response is affected more markedly than the ultimate accuracy of the response has been called *subcortical dementia.*[1] Cortical syndromes such as aphasia or agnosia are rarely seen.

The movement abnormality may precede or follow the mental disorder. Initially movements are few, choreic and may be brought out only when the patient is agitated. Later, they acquire an athetoid quality and affect the whole body. The gait has been described as 'dancing'. Speech may become dysarthric. Eye movements may be abnormal.

Pathology The characteristic feature of Huntington's disease is isolated involvement of the caudate nucleus. The head of the caudate nucleus atrophies due to selective loss of small 'spiny' GABA-ergic neurons.

Genetics Huntington's disease shows an autosomal dominant pattern of inheritance. The gene responsible is on the short arm of chromosome 4 and controls the synthesis of a protein called 'huntingtin'. The abnormality responsible for the disease appears to be an increase in the number of CAG triplet repeat sequences within the gene. It is now possible to determine if an individual has the gene. Testing of asymptomatic adults is however not ethically justifiable as currently there is no agent available to prevent or postpone the onset of symptoms. Testing is permissible for differential diagnosis or prenatal testing.

Investigations The diagnosis of Huntington's disease is supported by the evidence of caudate atrophy on CT or MRI. Functional imaging with SPECT or PET shows hypometabolism in the basal ganglia.

Treatment Unfortunately only symptomatic treatment is available. Neuroleptic agents (haloperiodol, thioridazine) may control the psychosis but can cause tardive dyskinesia on prolonged administration. Monoamine-depleting drugs such as reserpine and tetrabenazine may relieve chorea but do not help the psychosis and can exacerbate depression. An anxiolytic antidepressant such as trazodone may be useful.

Hemiballismus

This is a forceful, outward flinging of the affected limb which may be so violent that the patient injures the limb. The typical setting is an older patient who suffers a small ischemic stroke

[1] Subcortical dementia is a type of cognitive impairment seen in diseases which affect the basal ganglia and brain-stem leaving the cortex relatively intact. Besides Huntington's chorea, this pattern is also seen in progressive supranuclear palsy and multiinfarct dementia.

involving the opposite subthalamic nucleus. There may be associated or preceding hemiparesis. The hemiballismus usually subsides in a few weeks. Haloperidol may be beneficial.

Tics

A tic is a rapid, recurrent, purposeless semi-voluntary movement. Although they are not initiated by the patient, the patient may be able to suppress them for various periods of time with great effort requiring concentration. Tics disappear during sleep as do all the other involuntary movements described above. They are worsened by stress.

Tourette syndrome

Described by a French physician Gilles de la Tourette, the syndrome is characterised by multiple motor and vocal tics. The motor tics include facial grimaces, shrugging, kicking and blinking. The vocal tics may be grunts or 'swear words'. Because of the use of foul language this symptom is called coprolalia (fecal speech). The age of onset is 5 to 15 years. Intelligence is normal but there may be difficulties with sustained attention. The social stigma of this disease is considerable. There may be echolalia (repeating the examiner's words). Imaging and EEG results are normal. The genetics and pathogenesis of this syndrome are unclear. Partial relief is provided with medication. Drugs used include haloperiodol (0.25 to 2 mg bid) and pimozide (0.5 to 8 mg bid).

Tardive dyskinesia

Patients on long term treatment with neuroleptic drugs (e.g. chlorpromazine, haloperidol used for the treatment of schizophrenia) may develop involuntary movements that worsen with time and can persist even after withdrawal of the neuroleptic. The movements are typically facio-buccal-lingual masticatory dyskinesias[1] resembling Meige syndrome. Choreoathetoid movements of the limbs and 'foot tapping' may also be seen. A restless pacing (akathisia) is common. Treatment (to prevent worsening) consists of lowering the dose or if possible withdrawing the neuroleptic. Sudden cessation of medication is not only dangerous from a psychiatric viewpoint but may actually worsen the dyskinesia (withdrawal dyskinesia). There is no medication which can effectively control the movements. Hence, prevention is extremely important. Anti-psychotic medication should be used only when clearly indicated and even then at the lowest possible dose.

Myoclonus

Myoclonus refers to a sudden, jerky, shock-like contraction of a group of muscles. Myoclonic movements may be restricted to one group of muscles (segmental myoclonus) or may be generalised. Myoclonus may occur as a part of an epileptic phenomenon. These myoclonic seizures are discussed in the section on epilepsy. In some progressive dementias (SSPE, CJD and poliodystrophy), a periodic myoclonus is synchronised with periodic EEG abnormalities (cortical myoclonus). Myoclonus may be seen in metabolic encephalopathies. Essential myoclonus is a benign syndrome of autosomal dominant inheritance characterised by myoclonus but no other abnormalities. Movement induced myoclonus may be seen in patients recovering from anoxic encephalopathy and responds to clonazepam.

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[1] Fanciful names have been given to the type of dyskinesias seen: a sudden, brief protrusion of the tongue is called a 'fly-catcher's tongue' after the movement of a frog's tongue; the tongue protruding the cheek is called 'bon-bon sign' because it looks like the patient is sucking on a sweet.

KEY CONCEPTS

Parkinson's disease

- This is a slowly progressive degenerative disease characterised by slowness of movement, muscular rigidity, resting tremor, and postural instability.
- There is loss of pigmented neurons of *substantia nigra* and other brainstem dopaminergic cell groups. Secondary forms are related to the use of neuroleptics.
- The primary form has an onset in the sixth decade with a *pill rolling* tremor, *bradykinesia, festinant gait,* muscular rigidity and mask-like facies. *Micrographia* is characteristic. The onset is asymmetrical.
- The diagnosis is clinical.
- The MAO-B inhibitor *deprenyl* (selegeline) may slow disease progression. Levodopa with carbidopa provides substantial clinical benefit; *dopa-related dyskinesias* become evident after 2–5 years and the clinical response to levodopa diminishes. *Adjunctive* therapies include anticholinergic agents, amantadine and bromocriptine. Surgical implantation of fetal nigrostriate tissue or the patient's own adrenal medullary tissue are investigational modalities.

Essential tremor

- *Postural tremor* is most evident when the hands are held against gravity; the tremor is rhythmic, is not worsened by movement and is fine to coarse in quality. It may affect the hands, the head and the voice.
- β-blockers may be helpful.

Dystonia

- Dystonia is a sustained abnormal posture due to basal ganglia dysfunction. It may be *generalised (dystonia musculorum deformans;* linked to chromosome 9; childhood-onset) or *focal* (writer's cramp, blepharospasm, torticollis, oromandibular dystonia).
- Exclude Wilson's disease in an adolescent, and neuroleptic drug use in all age groups.
- Treatment with levodopa may be helpful in a subset of young patients with generalised dystonia. Injection of botulinum toxin is temporarily useful for localised dystonia.

Huntington's chorea

- This is an autosomal dominant condition (gene on chromosome 4) which has an onset after the age of 40 years. The pathological hallmark is a selective atrophy of GABA-ergic *spiny* neurons within the caudate nucleus.
- The clinical onset is with personality change, ataxia, choreiform movements, grimacing and hyperreflexia.
- A CT scan shows selective atrophy of the caudate nucleus.
- The treatment is with haloperidol or sulpiride for chorea. Adjunctive measures include phenothiazines, speech and occupational therapy, and genetic counselling.

9.8 Cerebellar ataxia

Structure and Function of the Cerebellum

The major function of the cerebellum appears to be motor. It may be described as the involuntary, fine tuning of all voluntary movements. Voluntary movements can be carried out if the cerebellum is diseased but the movements are clumsy and disorganised. The cerebellum maintains posture and balance, and controls the speed and trajectory of movements. Hence, symptoms of cerebellar dysfunction include disturbances of voluntary eye movements, speech, limb movements, stance and gait.

The cerebellum is located posterior to the brainstem to which it is connected by three cerebellar *peduncles.* The *superior cerebellar peduncle* joins the cerebellum to the midbrain and carries efferent fibres (fibres leaving the cerebellum). The *middle cerebellar peduncle* connects the pontine tegmentum to the cerebellum and carries afferent fibres entering the cerebellum) from the pontine nuclei. The *inferior cerebellar peduncle* connects the medulla to the cerebellum and brings afferent fibres to the cerebellum which come from the vestibular nuclei, the spinocerebellar tracts and the inferior olive in the medulla. Thus the cerebellum can integrate vestibular input and somatic sensations from the body with information regarding descending motor impulses from the cerebral cortex (through the pontine nuclei) and send back messages which modify the cortical output before it reaches the lower motor neuron. These efferent fibres pass through the *red nucleus* in the midbrain and the contralateral thalamus to reach the contralateral frontal lobe from where they are sent back down, with a second crossing over, to reach the limbs on the same side as the cerebellar lobe (of origin). Lesions anywhere along this track may cause symptoms similar to those caused by diseases of the cerebellum itself. The role of the *inferior olivary nucleus* in this process is not fully defined but must be an important one since many adult onset hereditary ataxias exhibit degeneration of this nucleus as an important abnormality on pathologic examination.

There are two ways in which the cerebellar structure can be viewed. One is based on embryology and the other on evolution. The *flocculonodular lobe*, the oldest part of the cerebellum phylogenetically, is the *vestibular cerebellum.* The anterior lobe, the second oldest, is the *spinal cerebellum.* The large new posterior lobe is the *pontocerebellum.* Clinically, there is a more useful distinction between the middle zone and the two lateral zones. Lesions of the middle zone (called the cerebellar *vermis*) cause disturbances of the trunk and the lower limbs. The symptoms include unsteadiness while sitting, standing and walking and *titubation* (involuntary nodding movements of the head). Lesions of the lateral zone (cerebellar *hemispheres*) lead to hypotonia and incoordination of ipsilateral limbs, a tendency to fall to the affected side, nystagmus (with a quick component to the side of the lesion) and dysarthria.

The cerebellar cortex on microscopic examination has three layers of cells: an *outer molecular layer,* a middle *Purkinje cell layer* (large pyramid-shaped cells) and an *inner granular layer.* The Purkinje cells seem susceptible to hypoxia, toxins and to selective degeneration. Inflammatory diseases destroy all three cell types. There are three important neurotransmitters in the cerebellum: glutamate and aspartate, which are excitatory, and gamma-aminobutyric acid (GABA), which is inhibitory.

Clinical Examination in Cerebellar Syndromes

The various motor abnormalities seen in cerebellar diseases are collectively called ataxia. As stated earlier, they affect the eyes, speech, trunk and limbs. Hypotonia of the affected limbs and *dysmetria,* which is a difficulty in controlling the range and velocity of a voluntary movement, are seen. Dysmetria is most marked towards the end of a voluntary movement when the most precise coordination is necessary. For example, one way of looking for dysmetria is the *finger-nose test,* where the patient is asked to touch the tip of his nose using his index finger and then to touch the tip of the examiner's finger which is held an arm's length away and to repeat this to and fro movement as fast as he can. There are different possible paths by which the patient's finger could reach the general area of his nose but touching the tip requires the kind of precision which is lacking in cerebellar lesions. Typically the patient's finger will move to and fro a few times, alternately overshooting and falling short of its target. This to and fro movement is called a *terminal intention tremor.*[1] Another manifestation of dysmetria is called *rebound.* The patient is asked to apply resistance against the examiner's hand and then the examiner suddenly removes her hand. The patient will not be able to easily stop his hand from moving in the direction in which he applied resistance. Care should be taken that the patient does not injure himself or the examiner. Another function of the cerebellum is to enable rapidly alternating or repetitive movements. This is tested by asking the patient to alternately slap the palm and then the dorsal surface of one hand on the palm of the other hand. In cerebellar disease such movements are slow and irregular. This is called *dysdiadochokinesia.* The patient's gait is broad-based. If the lesion is midline, the patient will tend to fall to either side and may even have difficulty in sitting without falling (*truncal ataxia*). In hemispheric lesions, the patient will fall to the side of the lesion. A subtle lesion is brought out by asking the patient to walk on a narrow base. The classical test for this is the *tandem walk* where the patient is asked to place the heel of one foot just in front of the toes of the other foot and thus walk forwards in a straight line. Patients with moderate to severe cerebellar gait ataxia hold on to a wall or person while walking. Other signs of cerebellar dysfunction include nystagmus and a dysarthria described as *scanning* (the patient breaks up words into irregular syllables: e.g. Ja-wa-har-lal). The handwriting becomes unsteady, and with large letters (*macrographia*). Tendon reflexes may be diminished and knee jerks may be *pendular.*[2]

Clinical Approach to Cerebellar Syndromes

When a patient presents with a cerebellar syndrome, the clinician should first ascertain the time course of the illness. An acute or subacute onset (over days, weeks or months) should make one consider acquired rather than inherited causes. This distinction is therapeutically important. Most inherited ataxias are presently not treatable. Classifying them will help in discussing prognosis and genetic counselling and is of importance for research, but will not appreciably change the patient's condition. On

[1] Dysmetria in the lower limbs is checked using a heel-shin test. The patient raises the heel of one foot and brings it down just below the opposite knee. He then slides the heel down the opposite shin till it reaches the ankle and then raises the heel back to the knee to repeat this procedure.

[2] When the knee jerk is tested with the patient seated, the leg swings back at least 3 times.

Table 9.18 Differential diagnosis of acquired cerebellar syndromes

Etiology	*Clinical features*	*Diagnosis*
Drug intoxication (anticonvulsants: phenytoin, carbamazepine, phenobarbital, primidone)	Nystagmus is the earliest sign followed by gait ataxia and intention tremor	History of seizures, drug intake; gum hyperplasia suggests phenytoin. Blood drawn for drug levels
Alcoholic	Gait ataxia is the most prominent feature as alcohol predominantly affects the anterior vermis. Upper limbs, speech and eye movements are less marked.	History; usually develops as an acute episode and may then remain unchanged; acute onset may or may not be as a typical Wernicke-Korsakoff syndrome. Rarely chronic alcohol abuse cause symptoms worsening over the years
Posterior fossa space-occupying lesion (abscess, tumour)	The patient may have symptoms and signs of raised intracranial tension	History, imaging (CT or MRI)
Paraneoplastic	Pure cerebellar syndrome with cancer of the lung, breast or ovaries. Rarely, a special syndrome of 'dancing' movements in the eyes and trunk–opsoclonus, myoclonus	Yo and Car antibodies on serological testing, X-ray chest and breast examination, gynecological evaluation
Viral encephalitis, post-infections, post-vaccinial	Usually there are other neurological signs including transient altered sensorium.	History, viral antibody titres may show acute rise but often the virus responsible is not identified
Stroke	Patterns described under stroke—lateral medullary syndrome, hemorrhage	History, imaging, later deficit remains static
Multiple sclerosis	Signs referable to the optic nerves, brainstem or spinal cord may be present	History of multiple episodes if present; abnormal MRI and VER
Slow-virus infections (CJD, SSPE)	Associated dementia is common; myoclonus, pyramidal signs may also occur	EEG may be abnormal

the other hand, distinguishing between the acquired ataxias is therapeutically important. The common types of acquired cerebellar dysfunction are outlined in Table 9.18.

If the history is of a gradual decline over years, a 'degenerative' disorder is likely.

HEREDITARY ATAXIAS

The hereditary ataxias are a group of slowly progressive, genetically determined degenerative disorders which share one common feature: so-called 'cerebellar' symptoms and signs which are a prominent part of the clinical syndrome.

Classification The classification of hereditary ataxias (Table 9.19) is a complex issue and neurologists are still working out the details of classification. A simple workable classification is outlined below.

1. The ataxia is classified as childhood-onset (beginning before age 20) versus adult-onset (beginning after age 20).
2. A detailed family history is taken. All available family members are examined. If relatives have been seen by other doctors their description is reviewed. Based on this the inheritance pattern is established: is the disease sporadic (no family history) or familial? If familial, is inheritance autosomal recessive, autosomal dominant or X-linked recessive. Most early-onset ataxias are autosomal recessive and most late-onset ataxias are autosomal dominant.
3. The patient undergoes a detailed general physical and neurological examination. Does this fit in with the pattern of a typical childhood-onset ataxia (Friedreich's ataxia) or a typical adult-onset ataxia as outlined below? If not, the patient is best classified as atypical and a neurological consultation should be sought. The important issue in the atypical ataxias is to differentiate between primary hereditary ataxias where the predominant manifestation is cerebellar dysfunction, and secondary or symptomatic cerebellar ataxias where there is an identifiable metabolic disease or defect causing the syndrome.
4. If the genetic trait or biochemical abnormality is known in a given family with hereditary ataxia, that information is also used.
5. The clinical manifestations should be carefully reviewed to ensure that ataxia is indeed the predominant neurological manifestation. If extrapyramidal or autonomic features are prominent, the disease may be **multisystem atrophy.**

Friedreich's Ataxia

The onset of symptoms is prepubertal. The inheritance pattern is autosomal recessive and is linked to chromosome 9. Ataxia begins in the lower limbs and progresses relentlessly to involve the upper limbs also. By the third decade (20s) the patient is usually unable to walk. Dysarthria is an early manifestation and horizontal nystagmus may be seen. There is a rapidly progressive loss of vibration and joint position sense (Romberg's sign[1] will be positive) in the lower limbs accompanied by the loss of deep tendon reflexes, intially the ankle jerk and later the knee jerk too. Some distal wasting and weakness, and extensor plantar responses are seen. Bladder control remains normal. Although not necessary for the diagnosis, pes cavus and kyphoscoliosis,[2] and progressive cardiomyopathy (usually hypertrophic and with arrhythmias) are frequently seen. Diabetes mellitus, deafness (sensorineural) and optic atrophy may occur.

Pathologically, the primary lesion is in the large sensory neurons of the dorsal root ganglion. These degenerate and their proximal processes (within the spinocerebellar tracts and posterior columns) and distal processes (large sensory peripheral nerve fibres) are secondarily affected. An EMG/NCV test is useful. Sensory nerve action potentials are not recorded in the lower limbs and are very slow in the upper limbs.

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[1] Romberg's sign is an inability to stand with the eyes closed.

[2] Asymmetrical muscle weakness in the growing years results in such deformities.

9.9 Neuromuscular disorders

NEUROMUSCULAR DISEASES— AN INTRODUCTION

The neuromuscular diseases which we are about to study used to be described as diseases of the peripheral nervous system. The so-called peripheral nervous system includes all the nerves and nerve cell bodies (ganglia) outside the confines of the brain and spinal cord, but it also includes their central connections. The nervous system functions as an integral whole, so the disorders of the peripheral nervous system may result in, or may be due to changes within the brain and spinal cord. Hence, disorders predominantly affecting the motor unit, peripheral sensory unit or the autonomic nervous system are referred to as neuromuscular diseases.

Anatomy of the peripheral nervous system

The typical *motor unit* is illustrated in Fig 9.21. Each motor unit consists of the cell body and axon of the lower motor neuron, the various muscle fibres innervated by this motor neuron, and the junction of the axon branches with the individual muscle fibres (the *neuromuscular junction*).

The peripheral sensory unit consists of 1) the sensory nerve terminals within the cutaneous (or proprioceptive) receptor and located in the peripheral nerve (the distal axon), 2) the sensory neuron cell body located within the dorsal root ganglion, and 3) the axon extending from the sensory neuron into the spinal cord through the posterior root (the central axon). The various components of the peripheral sensory unit are illustrated in Fig 9.22.

The autonomic nervous system may be divided into the sympathetic and parasympathetic fibre systems. The sympathetic nervous system consists of cell bodies in the intermediolateral column of the thoracic and lumbar spinal cord. Preganglionic axon fibres from these cell bodies leave through the *white rami communicantes* and enter the sympathetic ganglia. The cell bodies of the second order neurons are in these sympathetic ganglia located in the sympathetic chain extending along either side of the vertebral column. Postganglionic axon fibres arising from these second order neurons pass in the *grey rami communicantes* and through the visceral sympathetic plexuses to innervate the viscera and blood vessels. The parasympathetic preganglionic neurons lie in the brainstem and sacral spinal cord and their axons (the preganglionic axons) extend all the way upto the viscera. The postganglionic neurons are located in the wall of the viscus and they have short axons. The basic components of the sympathetic and parasympathetic nervous systems are outlined in Fig 9.23.

Classification of neuromuscular diseases

Disorders involving the lower motor neuron either alone or in association with the upper motor neuron are referred to as motor system diseases. The classical example of this group is the disease *amyotrophic lateral sclerosis* (ALS)

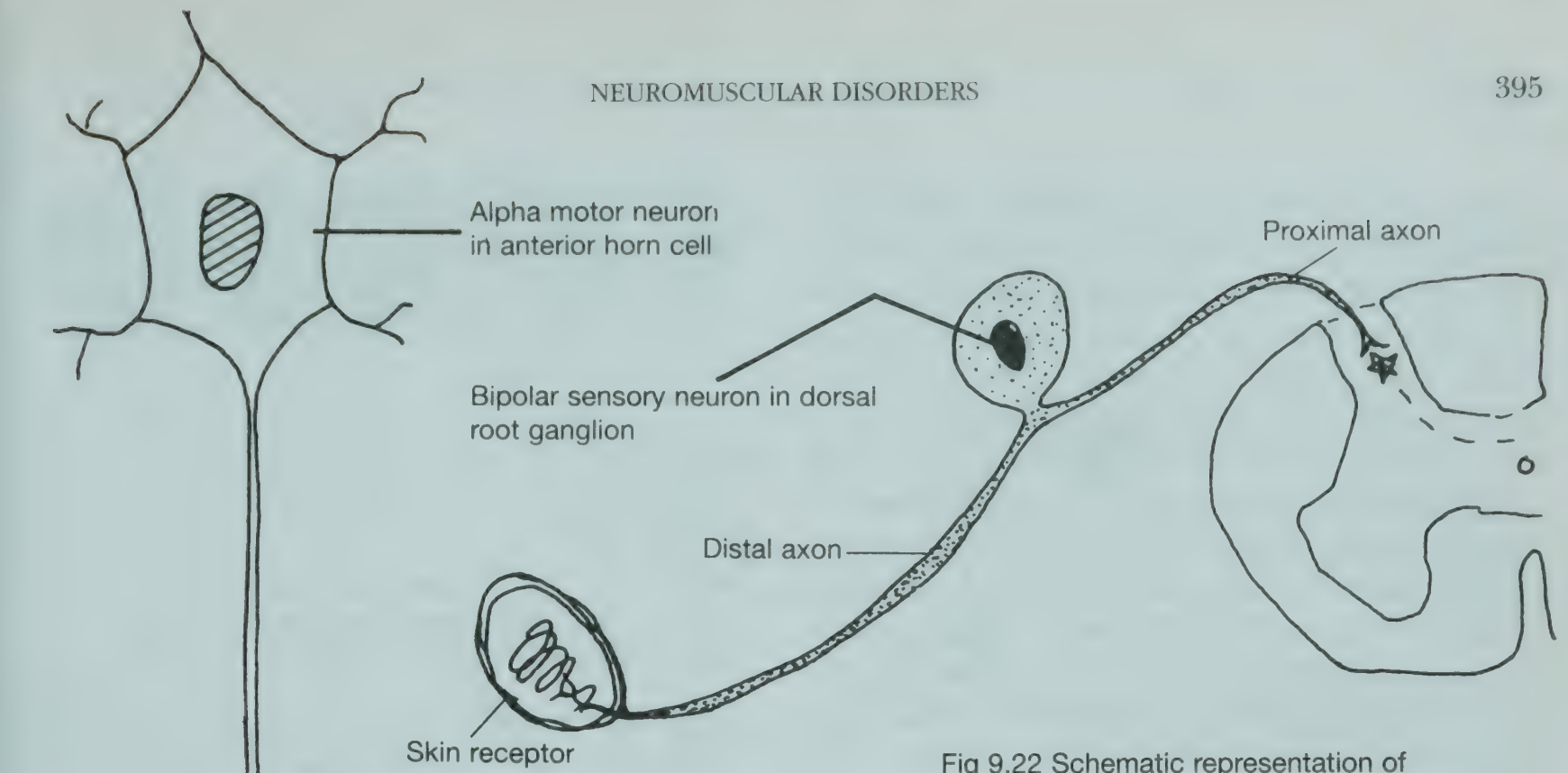


Fig 9.22 Schematic representation of peripheral sensory unit

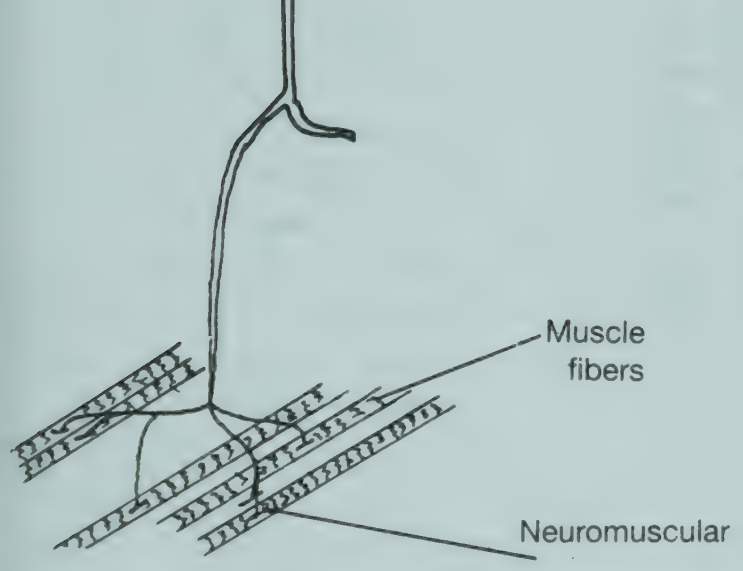


Fig 9.21 Schematic representation of a typical motor unit

and its variants. Disorders involving the axons (sensory, motor or autonomic), individually or in combination, are referred to as peripheral neuropathies. Disorders of the neuromuscular junction include *myasthenia gravis* and related conditions. We also have diseases which affect the skeletal muscles themselves known as myopathies and muscular dystrophies.

Structure and function of the skeletal muscle

The skeletal or striated muscle has a complex structure enabling it to convert chemical energy (derived from food through ATP and creatine phosphate) into mechanical energy in a precisely regulated fashion, thus enabling the maintenance of posture as well as of movement. Skeletal muscle fibres are syncytial cells formed by the fusion of multiple, uninucleated myoblasts during embryonic development. Each cell is surrounded by an endomysium. The numerous nuclei, mitochondria and glycogen granules are displaced to the cell periphery by myofibrils. *Myofibrils* are groups of regularly arranged bundles of thick and thin filaments. This regular arrangement gives each myofibril its striated appearence. The fundamental structural unit of the myofibril is the *sarcomere.* The ultrastructure of a sarcomere is illustrated in Fig 9.24. Muscle fibres are grouped into bundles called *fascicles*. Each *fascicle* is surrounded by a connective tissue sheath, the *perimysium*. The connective tissue sheath around the entire muscle is the *epimysium*.

Muscle fibres are classified as being either '*red*' or '*white*'. There is a difference in fibre colour because the red fibres have a larger number of mitochondria and hence, contain more pigmented mitochondrial cytochromes.

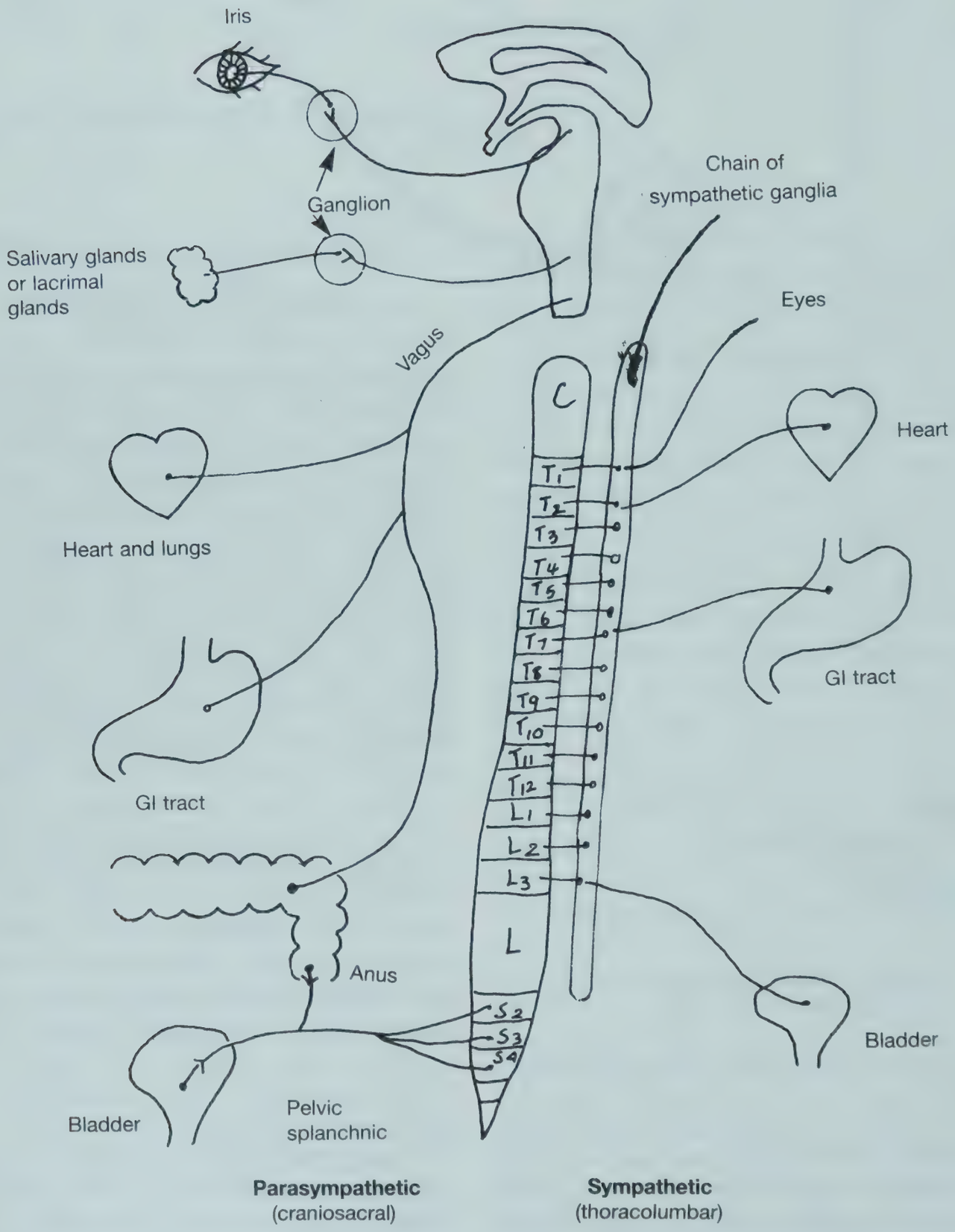


Fig 9.23 The autonomic nervous system

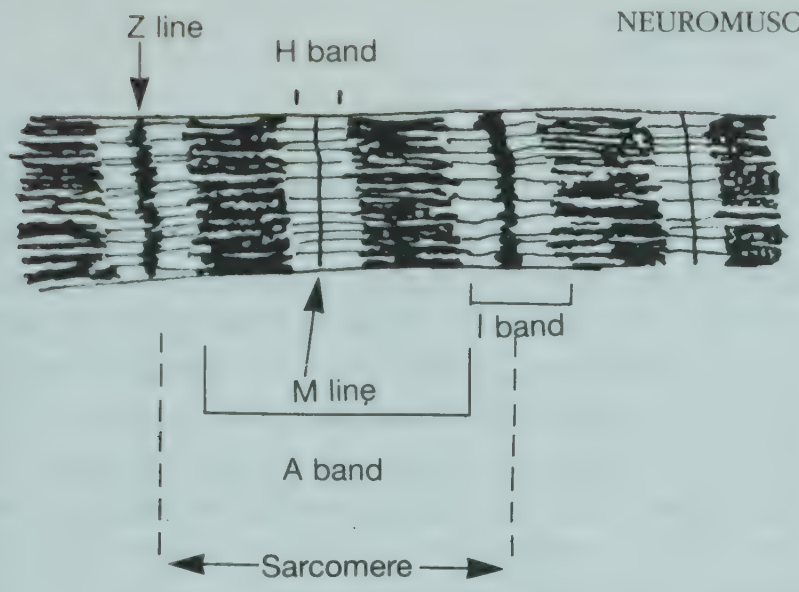


Fig 9.24 Components of the sarcomere

The red fibres derive energy for their contraction directly from the oxidative phosphorylation of ATP within the mitochondria. Hence they contract relatively slowly but are capable of prolonged contraction. These fibres are also called *Type I*, slow twitch or fatigue-resistant muscle fibres. They are innervated by smaller lower motor neurons which are easily activated (recruited) by low intensity efforts. Thus, these fibres are the first to begin and the last to cease contracting during any activity. White fibres derive energy for their contraction through anerobic glycolysis. They are capable of high intensity, rapid contraction under conditions of poor oxygenation; however, such contraction cannot be sustained. These fibres are therefore referred to as fatigue-prone, *Type II or* rapid-twitch muscle fibres.

Each skeletal muscle has abundant blood supply. Each myofibril is surrounded by an abundant, porous capillary network. This gives it access to the blood-borne nutrients it needs. However, it also exposes the muscle tissue to blood-borne toxins, parasitic organisms, immune complexes and immune-activated cells.

Structure and function of the peripheral nerves

The peripheral nerves are bundles of axons along with their insulating myelin sheaths and the connective tissue which surrounds and supports them. The peripheral nerves can have both myelinated and unmyelinated axons. The myelin in the peripheral nervous system is formed by circular wrappings of the surface membrane of Schwann cells around the axons and not from the oligodendrocytes. The myelin in the peripheral nervous system is therefore different from the CNS myelin in its embryological origin, physical and immunological structure and biochemistry. Not suprisingly, it also differs in its susceptibility to disease. The connective tissue covering of the peripheral nerve is in the form of three sheaths; from inside outwards these are the *endoneurium* around each nerve fibre,[1] the *perineurium* around each fascicle or bundle of nerve fibres, and finally, the *epineurium* which surrounds the entire nerve. Numerous blood vessels known as the *vasa nervorum* are present in this connective tissue. Disorders affecting these tiny vessels can result in ischemia of the adjacent nerve fibres. This is commonly seen in generalised vasculitic disorders such as polyarteritis nodosa.

The individual nerve fibres in a peripheral nerve are not all alike. Depending upon its cell of origin, an axon within a peripheral nerve may be classified as motor, sensory or autonomic. Nerve fibres also vary in diameter (from 0.2 μ to 20 μ) and in conduction velocity (from 0.5 to 120 m/s). The fastest conducting fibres have the largest diameter and the thickest myelin sheaths. In these fibres the distance between two adjacent *nodes of Ranvier*[2] (the internodal distance) is large. Since nerve conduction in myelinated axons proceeds by the generation of action potentials only at the nodes (a process called *saltatory conduction* [jumping from node to node]) the conduction velocity is proportional to the internodal distance. The large, rapidly conducting nerve fibres (with a diameter of 2–20 μ and conducting at the rate of 10–120 m/s), also called *Group A fibres*, include those carrying efferent impulses from the motor

[1] The term 'nerve fibre' designates the axon and when present, its myelin sheath.

[2] Schwann cell length is limited, so that a long axon may be myelinated by a long series of thousands of Schwann cells. The points where one myelinating Schwann cell ends and another begins are called the nodes of Ranvier. It is only at these points that the axon is exposed to the ions in the surrounding extracellular fluid.

neurons (both alpha and gamma) as well as those afferent nerve fibres mediating the sensations of touch, pressure, vibration, joint movement and some of the afferent fibres carrying pain and temperature sensations. Pain and temperature sensation along with all the visceral afferent sensations are also carried by small-diameter (0.2–1.2 μ), unmyelinated, slowly-conducting (0.7–2.3 m/s) *Group C fibres.*[1] The various fibres within a peripheral nerve may be differentially affected by a variety of illnesses.

The individual nerve fibres within a peripheral nerve do not run like taut strings from origin to termination. Instead, the nerve fascicles follow an undulating path interwoven with adjacent nerve fascicles. The structure of the peripheral nerve gives it strength with flexibility enabling it to withstand the various mechanical stresses that the nerve is subjected to during the movement of an adjacent joint; for example, the ulnar nerve as it crosses the elbow is stretched each time we flex our forearms.

A CLINICAL APPROACH TO NEUROMUSCULAR DISEASE

Clinical Symptomatology in Disorders of the Motor Unit (History)

The major symptoms of diseases affecting parts of the motor unit are fatigue and weakness of the muscles, wasting or enlargement of the muscles, involuntary muscle twitches, pain and stiffness of the muscle, muscle cramps and in rare cases, dark urine (due to myoglobinuria).

Chronic fatigue and easy fatiguability

The causes of generalised fatigue are numerous. They include unusual exertion, psychological stress, following any illness (post-viral syndrome), inadequate nutrition, anemia, pregnancy, occult systemic illnesses ranging from an infection such as tuberculosis to a malignancy such as lymphoma, metabolic disorders, cardio-respiratory disorders, liver disease (viral hepatitis, cirrhosis), renal disorders resulting in renal failure, as well as a variety of endocrine disorders. Generalised fatigue without any specific symptoms of muscle weakness or any other symptoms suggestive of neuromuscular disease is most likely not due to a neuromuscular cause. The one exception is myasthenia gravis (a disease often initially misdiagnosed) where the initial complaint may only be of generalised fatigue. However, on close questioning certain characteristic symptoms not found in the other disorders listed above are revealed. These symptoms include double vision, drooping eyelids, difficulty in swallowing and aspiration of food or liquids into the airway. They also include a marked improvement in muscle strength following even a very brief period of rest for the involved muscle.

Muscle pain

Muscular pain is a very common symptom. The commonly affected muscles are those of the shoulder (trapezius), calf (gastrocnemius), neck and lower back (erector spinae). An approach to the clinical differentiation of various muscle pain syndromes is outlined in Fig 9.25.

Three investigations of value in the differential diagnosis of muscle pain are 1. serum creatine kinase (CK) which becomes elevated when there is muscle damage (a normal value during an episode of pain is reassuring), 2. ESR-marked elevation may be seen in the inflammatory myopathies, and 3. urine examination for myoglobin (the presence of myoglobinuria suggests severe muscle damage); it is seen during episodes of metabolic myopathy.

Three important questions in the history are:

1. Where is the pain? (focal, multifocal or systemic)
2. When does it occur? (constant or intermittent; day or night; precipitating factors such as rest or exercise)
3. Are there associated symptoms? (muscle weakness; systemic symptoms such as fever, weight loss)

[1] Group B fibres consist of only the preganglionic axons to autonomic ganglia and have an intermediate diameter and conduction velocity.

Muscle weakness

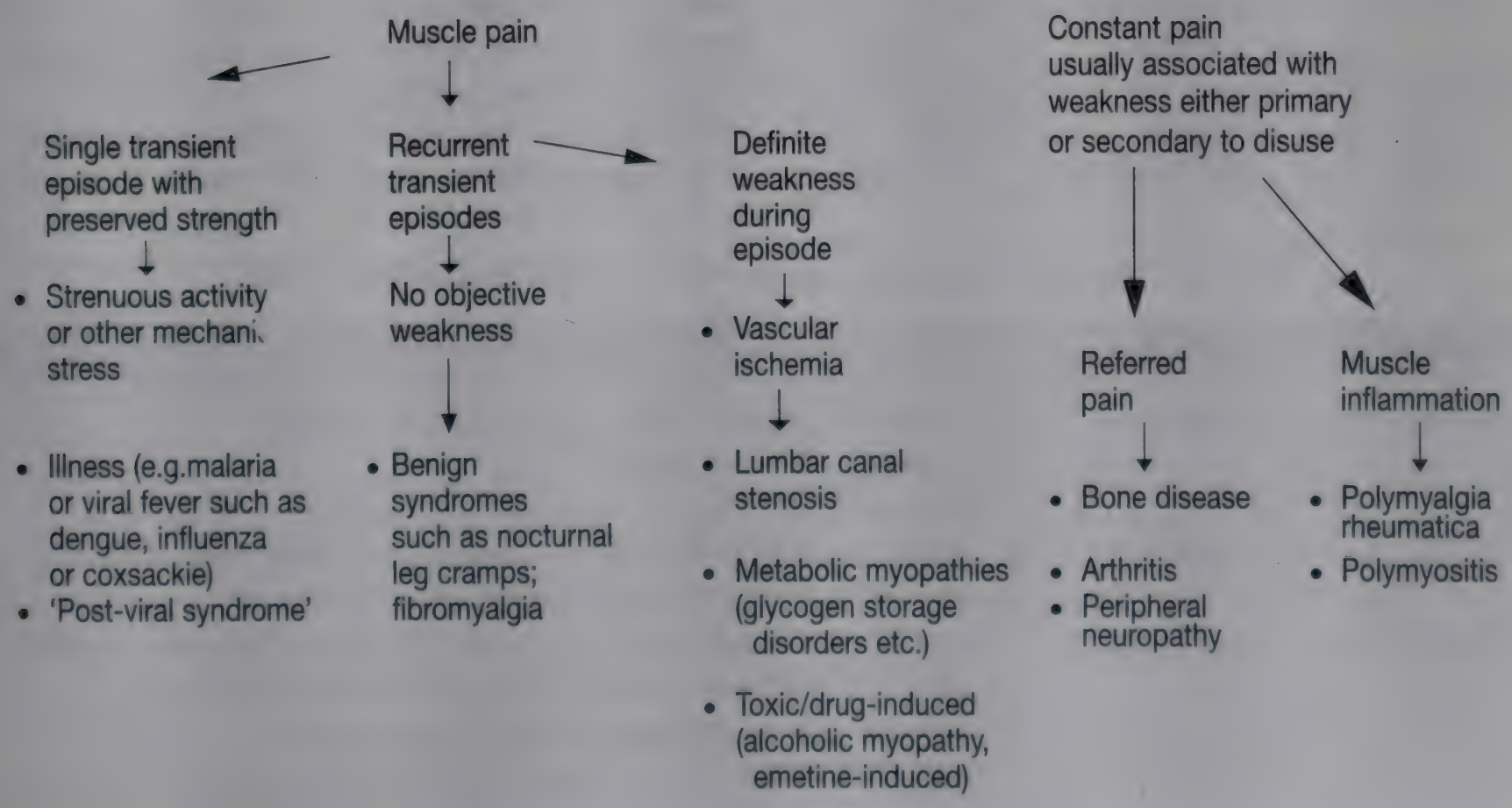
It is important to differentiate true muscle weakness from generalised fatigue. If the patient is unable to perform an activity which could earlier be performed with ease, then true weakness is likely. If this activity is one which most normal people could perform (such as climbing stairs, combing, dressing, feeding themselves or swallowing normal food) then true weakness is very likely.[1] Patients with true weakness are usually able to describe the specific symptoms which brought the weakness to their attention; for example, the patient may say, 'I noticed that I was unable to get up from the toilet without holding on to something.' The Indian toilet requires squatting down to floor level; 'difficulty in squatting' is an early symptom of developing lower limb girdle weakness in Indian patients. It is important to avoid asking leading questions until one is sure that the weakness described by the patient is real.

Particular care is needed to detect mild muscular weakness which is present from birth but is relatively progressive. Such a weakness may be seen in some of the congenital myopathies. In these patients, careful questioning of the parents (or grandparents) may reveal symptoms during gestation, infancy and early childhood, suggestive of muscle weakness. During this period of life, muscle weakness manifests as decreased muscle tone ('floppy baby syndrome', baby 'slipping through hands' when carried), decreased frequency of movements (reduced fetal movements, a hypoactive baby), or most importantly, delayed motor milestones. Failure to develop head control by 5 months or the inability to walk alone at 18 months is highly suggestive of a delay in motor development.

Once the presence of weakness is established, four important characteristics of the weakness must be determined historically. These are the pattern of muscle involvement, the mode of onset and speed of progression of the weakness, the temporal variation in the weakness, and family history.

[1] This statement assumes that non-neurological causes for this inability such as joint disease or severe depression have been excluded.

Fig 9.25 Clinical approach to muscle pain



The differential diagnosis of muscle weakness in provided in Table 9.20.

Pattern of weakness

It is important to determine which particular muscle groups appear to be maximally weak. Are the patients symptoms primarily referable to the ocular muscles, the facial muscles, the muscles of articulation (speech) and swallowing, the neck muscles, the trunk muscles or the muscles of the upper or lower limbs? With regard to the limb musculature it is important to determine whether the weakness is symmetrical or asymmetrical, proximal or distal. The most common symptoms in proximal muscle weakness of the upper limb include difficulty in raising objects, particularly heavy ones, above the level of the head, for example lifting an object down from the highest shelf. Other symptoms are difficulty in combing one's own hair (often marked in people with long hair), difficulty in hammering a nail into the wall (as in hanging a picture) and difficulty in carrying heavy things such as a bucket of water or a baby. The most frequent symptoms of distal weakness of the upper limb involve difficulty in gripping objects firmly and difficulty in the various fine activities required of the fingers, such as writing, sewing, knitting, dressing (for example, buttoning, unbuttoning, tying and untying cords, shoelaces) and cooking (for example, fine chopping). The chief symptoms of proximal muscle weakness in the lower limb include difficulty in squatting and getting up from a squatting position, difficulty in climbing stairs, running for long distances, frequent falls, changes in gait and finally, if weakness is severe, loss of the ability to stand. Weakness of the distal portion of the lower limb often manifests initially as a 'foot drop'.

Physical Examination in Disorders of the Motor Unit

Muscle atrophy and hypertrophy

The thinning of muscles is called *muscle atrophy.* Muscle atrophy is marked in anterior horn cell disease, moderate in those peripheral nerve disorders which affect the motor fibres, and absent in diseases of the neuromuscular junction. Muscle disease can cause muscular atrophy or enlargement. The enlargement of muscles is called muscular hypertrophy. When the muscles are enlarged but weak, it is called *pseudohypertrophy* and is usually the result of muscle fibres having been replaced by connective tissue or fat. The other causes of pseudohypertrophy include infiltration of the muscle with substances such as amyloid, or parasitic infestations such as cysticercosis. Focal swelling of a muscle may be due to trauma, tumour, or tendon rupture.

To estimate the size of the different muscles, it is important to have the patient undress

Table 9.20 Differential diagnosis of muscle weakness based on a temporal profile

Category	*Onset*	*Likely causes*
Acute	<24 hours	• toxins (botulism, snake-bite, aminoglycosides) • electrolyte disturbances • periodic paralysis
Subacute	over days	more common in disorders of peripheral nerve or neuromuscular junction e.g. Guillain-Barre syndrome (usual course)
Chronic	over months	amyotrophic lateral sclerosis, acquired neuropathies, myasthenia gravis, inflammatory myopathies, metabolic myopathies
	over years	spinal muscular atrophy, inherited neuropathies, congenital myopathies, muscular dystrophies

adequately and to compare the two sides, the upper limbs with the lower limbs and the proximal musculature with the distal musculature. This is important because muscle bulk varies widely among normal people depending on their age, sex and degree of physical activity. Changes in muscle bulk indicate longstanding disease. Subtle differences between the two sides are best appreciated by careful measurement of the circumference of the limb. Such measurements also provide an easy tool for repeated follow-up over time. The point at which the circumference is measured should be defined in relation to a bony landmark; for example, 'with the ankle in a neutral position, the circumference of the calf at 'x' cm below the tibial tuberosity, is 'y' cm.' The contour may also help in detecting muscle atrophy. For instance, atrophy of the deltoid leads to 'squaring' of the shoulders, atrophy of the serratus anterior leads to 'winging of the scapula' and atrophy of the interossei leads to 'hollowing' of the spaces between the extensor tendons.

Muscle tone

Disorders of the anterior horn cell and peripheral nerve cause hypotonia and diminished tendon reflexes. However, muscle tone may be increased and tendon reflexes exaggerated in amyotrophic lateral sclerosis because of the concomitant involvement of the upper motor neurons. Muscle tone and tendon reflexes are typically normal in disorders of the neuromuscular junction. In muscle disease, the decrease in muscle tone is proportionate to the degree of weakness.

Muscle power

For a screening examination of muscle power the ability to perform common tasks is noted. For evaluating power in the lower limbs, the patient is asked to remove footwear and walk. After observing the basal gait, the patient is asked to walk first on his heels and then on his toes. The ability to rise from a chair while holding the arms folded across the chest and the ability to step up on to a chair are good indicators of the normal function of the hip extensors and flexors. Weakness of the hip abductors will present as a waddling gait. Distal weakness of the lower limb presents as an inability to walk on one's heels or toes and if the weakness involves the dorsiflexors of the ankle there is a foot drop and a high stepping gait. Other tests of weakness of the lower limb musculature include the ability to hop on either foot, rise from a squatting position and fully extend the knee against gravity; knee extension lag noted while standing indicates weakness of the quadriceps.

The strength of the hand muscles can be judged by asking the patient to grip the second and third fingers of the examiner's hand,[1] or to squeeze a rolled sphygmomanometer cuff. Other screening tests for power of the upper limb muscles include checking strength during shoulder abduction, flexion and extension of the elbow and forearm pronation and supination.

When a lesion affects a specific region (such as one lower limb or only one hand) it is essential to test the individual muscles in that limb. Details of such testing can be found in books on clinical examination.

Muscle strength is graded on a 0 to 5 scale[2] where 5 indicates normal power; 4 the ability to move against some resistance; 3, the ability to contract against gravity but not against any additional resistance; 2, the ability to move in the absence of gravity; 1, where the occasional flicker of contraction is seen; and 0, when there is no movement.

Category 4 has been criticised for being very broad and includes muscle strength ranging from 50 to over 90 per cent of normal. Therefore, it is sometimes useful to subdivide this category into 4+ and 4– or to provide an additional verbal description such as 'power in the lower limbs is

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[1] Asking the patient to grip three fingers may hurt the examiner!

[2] This scale is called the MRC scale because it was developed by the Medical Research Council, U.K.

4/5 in all the muscle groups with the left limb being weaker than the right'. While testing for muscle strength it is important to make allowances for age, sex, occupation, illness, and motivation. Comparison of the two sides is useful in detecting an asymmetric process but mild asymmetry may be a consequence of hand preference.

Muscle fasciculations

Fasciculations are visible involuntary contractions of a group of muscle fibres belonging to one motor unit. To look for muscle fasciculations requires patience. The limb should be warm and rested. Persistent contractions of one muscle in a rhythmic fashion (such as the eyelids) is suggestive of *benign myokymia.* On the other hand, brief, sudden, and sporadic contractions which move from muscle to muscle indicate a more serious disorder.

Myotonia

Myotonia manifests clinically as a sustained contraction of the involved muscle with an inability to relax the muscle. Myotonia may be elicited by voluntary contraction, percussion or cold. It is demonstrated by the patient's inability to rapidly release her grip after a handshake. Percussion myotonia is noted by tapping the thenar eminence or on the tongue (by using two tongue depressors and a knee hammer).[1]

Table 9.21 summarises the differences between an upper motor neuron syndrome and a lower motor neuron syndrome.

Clinical Symptoms in Disorders of the Sensory Unit

Disorders of the peripheral sensory unit can result in abnormal sensory phenomena (positive symptoms) or sensory impairment (negative symptoms). Positive phenomena (*paresthesia* or

[1] To look for percussion myotonia in the tongue, a tongue depressor is placed horizontally beneath the slightly protruded tongue to protect it from the lower teeth; another tongue depressor is made to lie 'on end' on the upper surface of the tongue directly above the first. The upper tongue depressor is lightly tapped on top with the knee hammer and quickly removed. A dimple is noted along both lateral margins of the tongue at the site where it was percussed.

Table 9.21 Comparison of upper and lower motor neuron lesions

Feature	*Upper motor neuron lesion*	*Lower motor neuron lesion*
Pattern of weakness	paresis of movement (e.g. hip flexion, shoulder abduction) rather than of individual muscles or muscle groups	paralysis of individual muscle or groups of muscles
Muscle tone	increased tone (spasticity); the exception is the acute stage of spinal shock when tone may be decreased	decreased tone (flaccidity)
Muscle bulk	normal; mild atrophy may be seen with disuse (disuse atrophy)	muscular atrophy
Deep tendon reflexes	increased, clonus may be present	decreased or absent
Superficial reflexes	decreased or absent	unaltered
Plantar responses	extensor	flexor
Jaw jerk	may be brisk	unaltered
Abnormal muscular movements	none unless extrapyramidal system involved	fasciculations, myotatic irritability

dysesthesia) are described in various terms. The patient may describe them as similar to the tingling felt as the limb is recovering from 'sleep' or as a more painful sensation. Sometimes the impulses arising at the regenerating tip of a traumatised nerve fibre may result in pain projected into an anesthetic or amputated limb; in the latter case, the pain is called *phantom pain*. On clinical examination, positive phenomena may be present in the absence of a demonstrable abnormality. Sensory impairment may involve the impairment of all sensory modalities and may be complete (*anesthesia*) or partial (*hypesthesia*). Hypesthesia manifests as both an elevation in the threshold of perception and a diminution in perceived stimulus intensity. Sensory impairment may also be modality-specific. If Group C fibres alone are involved, there is an impairment in sensations of pain and temperature, with relative preservation of other modalities (*small fibre neuropathy*). The presenting symptoms include noticing an absence of pain with a minor injury (such as a cut on the fingertip), being unaware of the temperature of water (such as during a bath), or sustaining frequent minor burns during cooking. With severe sensory impairment there may be painless non-healing ulcers on the extremities. The feet are particularly vulnerable.

If there is relatively isolated involvement of the large proprioceptive fibres, impaired perception of vibration may be the earliest sign. The patient may complain of unsteadiness while walking, particularly in dim light, and will have a tendency to trip over small objects. Severe proprioceptive sensory loss may lead to joint deformities (*Charcot's joints*).[1]

Since touch is mediated by both Type A and Type C fibres, it is usually impaired as part of a generalised sensory impairment. The patient may describe an inability to feel the contour of the ground while walking barefoot or a sensation of 'walking on cotton wool.' Tasks involving intact sensory perception in the fingertips, such as, discerning textures or reading Braille, may be affected.

[1] Causes include diabetes mellitus, syringomyelia, syphilitic tabes dorsalis, leprosy, amyloidosis, and intraarticular glucocorticoid injections.

Physical Examination in Disorders of the Sensory Unit

Touch is tested using a ball of cotton wool or a light stroking movement with the examiner's fingertips. The two sides of the body should be compared. The subject may be asked to close her eyes and say 'yes' every time a stimulus is felt. By varying the stimulus intensity, the examiner can measure the threshold for the sensation. This may be quantified using an *aesthesiometer.* The patient can also be asked to grade the perceived intensity of the stimulus as compared to the stimuli applied to other body areas. While comparing different body parts it should be remembered that certain areas are normally more sensitive than others. Thus, a difference in sensory perception between the dorsum and the sole of the feet is normally seen because of the greater skin thickness over the plantar surface. A mild (less than 10 per cent) or inconsistent hypesthesia may not be real. If a sensory impairment is detected its borders should be mapped starting within the area of hypesthesia and proceeding outwards with multiple, closely placed stimuli until the patient reports a return of normal sensation. Pain may be tested using a pinprick stimulus. The stimulus intensity should be sufficient so that the patient perceives it as a prick (rather than as a touch) but should not be so great that the skin is breached. Temperature is tested using a conical flask filled with water at a given temperature. If test tubes are used, the entire length of the tube should be applied to the skin as the rounded bottom is too small a stimulus surface for accurate temperature perception. Vibration is tested using a 128 Hz tuning fork. While testing joint position sense, the patient may be asked to indicate the direction of movement, either verbally or by mirroring the movement in another limb. In the

same fashion, she may be asked to indicate the final position reached. Joint position sense is usually tested in the great toe and the fingers, although any joint may be tested. In the case of the great toe, the examiner's thumb and forefinger are placed on either side of the toe (rather than on the top or bottom) to avoid giving clues by way of the cutaneous receptors. Abnormalities of 'deep' sensation (proprioception) may result in clumsiness of movement particularly with the eyes closed. The manifestations of this *sensory ataxia* may include an intention tremor in the upper limb and unsteadiness of gait. *Romberg's sign* is positive, which means that although the patient is able to stand with feet close together and eyes open, the patient may sway or fall upon closing the eyes.

Sensory examination is less reliable if the patient is fatigued, has cognitive problems, or has altered sensorium. Since a sensory examination is subjective, one should be alert to the possibility of malingering or of a conversion reaction. Clues to a non-organic cause include a sharply-defined sensory deficit with a non-physiological boundary (such as the midline of the trunk), a 'no' response to indicate that the stimulus is not felt, or a failure to reliably localise the anesthetic patch (outlined with ink) when two or more examinations are done at least 15 minutes apart. In a patient without neurologic complaints the sensory examination may be abbreviated to an assessment of touch, pinprick and vibration over the hands and feet and a Romberg's maneuver.

Hyperpathia is defined as an excruciating sensitivity to sensory stimuli and may be present despite an increase in the sensory threshold.

Symptoms and Signs of Dysfunction of the Autonomic Nervous System

The autonomic nerve fibres in the peripheral nerves are typically involved in conjunction with the small sensory fibres because they share similarities in structure and physiology. The affected limb may show atrophy of the skin, hair loss, coldness, and decreased sweating. The *starch test*[1] may be used to outline an area of decreased sweating due to a peripheral nerve lesion. Severe autonomic and sensory neuropathy when present together can result in bone resorption and this may be seen in leprosy, and hereditary sensory neuropathies. If there is generalised autonomic dysfunction, this can be detected by measuring the change in blood pressure and heart rate between the seated and standing postures. A fall in systolic blood pressure of more than 20 mmHg or a fall in diastolic pressure of more than 10 mmHg on changing from recumbent to the erect position suggests postural or orthostatic hypotension; the heart rate should simultaneously increase in normal people by 10–30 beats/min. The pupils and bladder should also be examined.

DIAGNOSTIC PROCEDURES IN NEUROMUSCULAR DISEASES

Muscle biopsy

Muscle biopsy is a procedure wherein a small piece of muscle to be examined pathologically, is removed either surgically or by using a percutaneous 'punch' biopsy. It is used to diagnose muscle diseases (dystrophies, myositis, mitochondrial myopathies), detect vasculitis and abnormal storage products in metabolic disorders and may show that a given patient has muscle weakness secondary to lower motor neuron or nerve disease (*neuropathic* changes).

A 'mild to moderately' affected muscle is chosen for biopsy since this maximises the chances of finding an abnormality. A markedly atrophic muscle may show only fat and fibrous tissue. A muscle which has been recently traumatised by an EMG needle must not be

[1] Powdered starch and iodine are applied to the limb being tested and sweating is induced by placing the patient in a warm atmosphere or giving him hot tea. The moisture in the sweat dissolves the starch and iodine enabling their chemical reaction and a change in colour from brown to dark blue.

biopsied; such a biopsy is likely to have artifacts. Muscle biopsy is usually performed under local anesthesia. An incision is made in the skin, the superficial and deep fascia, and the muscle is reached. A muscle fascicle approximately 1 to 2 cm in size is chosen. It is teased out and the ends of the muscle fascicle are tied before removal. The removed muscle is stretched out over a firm surface such as a part of a tongue depressor to prevent contracture artifacts. The muscle biopsy specimen is divided and processed in three parts: two portions are placed respectively in formalin (for conventional microscopy) and in glutaraldehyde (for electron microscopy), and a third part is frozen in liquid nitrogen (for immunohisto-chemistry and biochemical studies). Side effects of the procedure include local pain and hematoma formation (which may be avoided by attention to hemostasis).

The findings on pathological examination of the muscle are changes in myofibre size, shape, ratio of fibre types, and changes in the connective tissue between fibres. Three basic patterns are distinguished: *neuropathic* pattern, *dystrophic* pattern and the *myositis* pattern.

Neuropathic pattern: A denervated muscle fibre undergoes atrophy, and becomes angulated as it is squeezed by adjacent fibres. The surviving motor axons sprout collaterals and reinnervate adjacent atrophic fibres. Usually, muscle fibres supplied by one motor axon are randomly distributed amongst fibres supplied by other axons.

When the number of axons diminishes and reinnervation occurs, there is grouping of all the fibres supplied by the same axon, and hence having the same fibre type (Type I or Type II). The axon supplying this enlarged motor unit may subsequently die resulting in a group of atrophic fibres (*grouped atrophy*). A denervated muscle shows muscle fibres of two sizes (bimodal distribution), that is, atrophic and normal.

Dystrophic pattern: In muscle dystrophies, the muscle fibres become damaged and die. Necrotic fibres appear eosinophilic and rounded, with pyknotic nuclei. The invading macrophages may be seen phagocytosing the muscle fibres. In the early stages, regenerating muscle fibres are seen. These are small, and basophilic (due to increased amounts of RNA) and have large vesicular midline nuclei. In the later stages, regeneration fails and the muscle fibres are replaced by fat and fibrous tissue. The fibre diameters have a broad range (from atrophic to hypertrophic) but the distribution is *unimodal.* Angulated fibres and grouped atrophy are not seen.

Myositis pattern: The most characteristic feature is the presence of inflammatory cell infiltrates in the muscle. Typically, these are lymphocytes seen around blood vessels and in the connective tissue between muscle fibres. Very active necrosis and regeneration are seen. In polymyositis, this activity is distributed throughout the muscle fascicle, whereas in dermatomyositis it is predominantly peri-fascicular (at the outer margins of the fascicle). The fibre diameters show a narrower distribution than in muscular dystrophy but the pattern is unimodal. There is less fatty infiltration as the process is more acute. Vasculitis may be seen in patients with polyarteritis nodosa and granulomas may be present in sarcoidosis. In patients with parasitic infestation, the detection of a cysticercus or a trichinella larva may establish the diagnosis.

Any condition resulting in muscle disuse causes preferential atrophy of Type II fibres. Selective atrophy of Type I fibres is seen in myotonic dystrophy. Other changes in muscle structure can only be seen using special stains or with electron microscopy, and these are described under the specific conditions.

Nerve biopsy

Nerve biopsy involves the removal of a small piece of peripheral nerve for pathological examination and can show demyelination, axonal degeneration, vasculitis, inflammation and infection (as in leprosy, sarcoidosis), and

deposition of abnormal substances such as amyloid. The nerve most often biopsied is the sural nerve because it is frequently affected by pathological processes, is easily accessible and resection of the nerve causes only a minor sensory impairment (over the lateral margin of the foot) with no motor weakness. If the clinical examination or an EMG suggests that the sural nerve is affected, the yield on biopsy is high. In patients who have disease localised to other nerves which cannot be removed for biopsy (like the ulnar nerve), fascicular biopsy (that is, removing just a few fascicles) has been attempted. This is harder and more likely to cause procedure-related neurological deficits than sural nerve biopsy.

In addition to standard preparations, special thin sections (1μ thick) and teased single-fibre preparations are often examined. Evidence of demyelination and remyelination (thin myelin sheaths and onion-bulb formation) is sought. In axonal regeneration, nerve sprouts (clusters) may be seen. In teased nerve preparations remyelinating fibres show a decreased internodal distance.

Nerve conduction studies

The conduction of electrical impulses along a peripheral nerve is an index of the functional integrity of the nerve. Two surface electrodes are placed over the nerve, one proximally and another distally. If the nerve is a motor nerve, a recording electrode is placed over the belly of a muscle innervated by the nerve; the nerve is stimulated first proximally and then distally and the resulting muscle contraction recorded (*compound muscle action potential*). If it is a sensory nerve, a stimulating electrode is placed distally in a region innervated by the nerve ; this electrode is activated and the resulting nerve impulse (*sensory* nerve action potential) is recorded from the distal and proximal nerve electrodes. The proximal and distal latencies are determined (by measuring the time from stimulus artifact to the recording of the action potential) and the difference between the two is divided by the distance between the electrodes, to estimate the conduction velocity of the nerve. Nerve conduction velocities in adults range from 40–80 m/sec. The amplitude of the compound muscle action potential is usually 5–10 millivolts and that of the sensory nerve action potential is 10–50 microvolts. Since the velocity of nerve conduction depends on the conduction velocity of the fastest fibres within the nerve, it is abnormal in demyelination which involves the large myelinated fibres. The amplitude of the action potential depends on the total number of fibres stimulated. Hence, axonopathies may not affect the velocity but may cause a low amplitude, broad (or dispersed) action potential. In severe demyelinating disease, the amplitude of the action potential can diminish. With focal demyelination, the amplitude may diminish so markedly that no electrical activity is detected downstream (*conduction block*).[1] The *distal latency* is defined as the conduction time from the most distal electrode to the recording or stimulating electrode. Normal values for distal latency are available. In conditions like the carpal tunnel syndrome, the distal latency is abnormal.

Nerve conduction in the proximal segments of the nerves and nerve roots can be studied using special motor responses called the *F wave* and the *H reflex*. The F wave can be recorded from any muscle. When a supramaximal stimulus is given, an action potential travels up the nerve and ventral root to the motor neuron, and is reflected back down to the muscle causing a delayed motor contraction. An H reflex is recorded in the soleus muscle using a submaximal stimulus. The action potential travels in the proprioceptive sensory fibres within the nerve, through the dorsal root and a monosynaptic reflex arc, to the motor neuron, resulting in a late muscle contraction. This is sensitive for detecting an S1 radiculopathy.

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[1] A drop in amplitude of >50% is sufficient to indicate a conduction block.

Electromyography

The electromyogram (EMG) is a procedure in which a needle electrode is inserted percutaneously into a muscle. The electrical activity within a small area of muscle around the needle tip is recorded during relaxation and with different grades of voluntary contraction of the muscle. This electrical activity can then be displayed on a cathode ray oscilloscope and made audible using a loudspeaker. The image at different times can also be recorded on paper. The EMG is an extension of the clinical examination. The clinical examination determines which muscles are to be examined (electromyographically) and how the EMG findings are to be interpreted.

As an individual muscle fibre contracts, the stimulating action potential travels from the neuromuscular junction towards the poles of the muscle fibre. This is recorded as a negative (upward) monophasic deflection called a *fibrillation.* Monophasic positive deflections, called positive *sharp waves,* are also caused by the contraction of individual muscle fibres. More commonly, all the muscle fibres of a given motor unit contract simultaneously and the summation results in a triphasic waveform called the *motor unit action potential* (Fig 9.26). There is an initial small positive deflection followed by a larger negative deflection which transiently overshoots and gradually returns to the baseline. As the degree of contraction increases, more and more motor units are recruited and finally the individual motor unit potentials occur so close together that an *interference* or *recruitment pattern* results. At rest, the normal muscle is electrically silent. The trauma of needle insertion may cause a few fibrillatory potentials (*insertional activity*) which rapidly disappear.

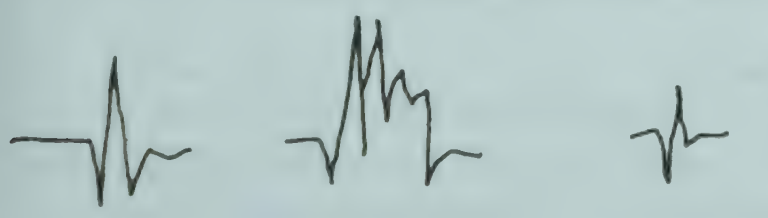


Fig 9.26 Motor unit action potentials

Patterns of EMG abnormality: An EMG can be used to detect abnormalities of resting muscle activity, muscle disease, muscle denervation, diseases of neuromuscular junction, diseases of the upper motor neuron, and movement disorders.

Increased insertional activity occurs when there is muscle inflammation (as in polymyositis). In a condition called *myotonia,* the sarcolemma is irritable and muscle contraction may occur without an impulse from the motor axon. The EMG pattern in myotonia is a high frequency, repetitive discharge that waxes and wanes in both amplitude and frequency, producing a sound like the revving of a motor cycle engine. This has also been called a *dive-bomber* sound.

As muscle denervation occurs, a *neuropathic pattern* is seen on the EMG. Some motor units drop out and the recruitment pattern is less dense (reduced interference). With reinnervation, the remaining motor axons innervate adjacent muscle fibres so that the motor units are larger and the individual motor unit action potentials becomes high amplitude, prolonged and polyphasic. The sarcolemma of a denervated muscle becomes more excitable than normal. Similarly, a damaged axon may fire, resulting in the contraction of a single motor unit in the absence of voluntary contraction. The former results in a *fibrillation potential* while the latter causes a single small motor unit potential which is called a *fasciculation.* Fasciculations are particularly common in motor neuron disease.

In intrinsic muscle disease a *myopathic pattern* is seen on the EMG. Since the total number of motor units has not decreased, a normal interference pattern occurs but this happens at a lower amplitude on the EMG and at a lower intensity of the voluntary contraction as measured clinically. This is called *early recruitment.* Fibrillations may be seen at rest if one portion of a muscle fibre is separated from its innervated portions by segmental necrosis. Fasciculations are not seen. Since scattered muscle fibres are destroyed within each motor

unit, the motor unit potentials are of lower amplitude and shorter duration.

Newer specialised techniques permit the recording of the EMG from single muscle fibres (*single fibre EMG*) or from an entire motor unit (*macro EMG*).[1] Special EMG techniques may also be used to assess the degree of spasticity (*central EMG*). Simultaneous EMG recordings from pairs of agonist and antagonist muscles are useful in evaluating the types of tremor (*tremorogram*), differentiating asterixis from tremor and determining the type of myoclonus. For the purposes of a tremorogram, and sometimes in children, a surface EMG may be sufficient where the electrode is strapped on to the skin overlying the muscle (instead of using a needle).

Some uses of electrodiagnosis in neuromuscular disorders (EMG/NCV) are:

1. to objectively document a pure sensory nerve lesion or denervation in a patient with questionable symptoms;
2. to detect subclinical involvement, for example, in siblings of the proband;
3. to distinguish a root or plexus lesion from more distal involvement;
4. to distinguish between axonal and demyelinating peripheral neuropathies;
5. to distinguish between a polyneuropathy and a mononeuritis multiplex pattern;

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Amyotrophic lateral sclerosis[2] or *motor neuron disease* is a progressive degeneration of all the motor neurons and affects both the 'upper' and the 'lower' motor neurons. It is sometimes divided into four subtypes. The commonest types are typical amyotrophic lateral sclerosis affecting the spinal motor neurons (causing wasting *amyotrophy*) and the upper motor neuron fibres in the lateral corticospinal tracts (*lateral sclerosis*). Less frequently, there is an almost exclusive involvement of the spinal motor neuron resulting in *progressive spinal muscle atrophy*. When the motor nuclei of the lower brainstem (cranial nerves V-XII) alone are affected it is called *progressive bulbar sclerosis.* There is also an extremely rare variant, with exclusive upper motor neuron involvement, known as *primary lateral sclerosis.*

Epidemiology Incidence of amyotrophic lateral sclerosis is approximately 1 per 100,000. Men are affected more frequently than women. Amyotrophic lateral sclerosis is a disease of late adulthood (usually after the age of 50 years). A variant of the disease called *amyotrophic lateral sclerosis-dementia-Parkinsonism complex* was found to be very frequent in the Pacific island of Guam. The probable etiology was a toxin in the cycad nut[3] consumed by the local people. The incidence of this syndrome in Guam is now decreasing.

Pathogenesis Amyotrophic lateral sclerosis shows familial clustering in only 5–10 per cent of patients. However, the nature of the environmental risk factors is as yet unknown except for the small cluster seen in Guam. The disease has not been linked to any infectious agent.

Excitotoxic injury, that is, damage to the neurons secondary to excessive levels of the excitatory amino acids (glutamic acid and aspartic acid) is known to be a step in the pathophysiology of the disease. A familial form of ALS has been associated with abnormalities in the superoxide dismutase gene.

Pathology Motor neuron cells within the brainstem nuclei and the ventral horn of the spinal cord undergo chromatolysis and die. Eosinophilic cytoplasmic inclusion bodies called

[1] In conventional EMG only those fibres of motor units that are within a 50 μ area around the needle tip contribute to the motor unit action potential.

[2] Amyotrophic lateral sclerosis is also called motor neuron disease. Other names include, Aran-Duchenne disease or Charcot's disease after the physicians who first described the disease and Lou-Gehrig's disease after a famous baseball player who unfortunately died of the disease.

[3] The toxic agent is supposed to be an excitatory amino acid: BMAA, *beta-N-methylamino-L-alanine.*

Bunina bodies may be seen within the motor neurons. There is a loss of large pyramidal cells in the motor cortex. The motor neurons of the oculomotor system and the parasympathetic neurons innervating the sphincters of the bowel and the bladder are always spared.

Secondary to the loss of the motor neurons, the ventral roots of the brainstem and the spinal cord atrophy. Initially motor units grow larger as the remaining motor neurons try to innervate as many muscle fibres as possible. Finally, there is extensive atrophy of all the muscles as they become denervated.

Clinical features The clinical symptoms are early prominent wasting which is more marked distally than proximally. Weakness and fasciculations are other prominent features. Upper motor neuron signs include spasticity and hyperreflexia. Brainstem involvement results in dysphagia and dysarthria; this along with involvement of the respiratory muscles, is usually the cause of death. Ocular motility, sensations, bladder function and intellect remain intact until the end. The median survival is 3–5 years and the course leads inexorably downhill.

Treatment Physical therapy and rehabilitative measures including mechanical aids, communication aids, speech and swallowing therapy are beneficial. In the later stages of the disease nutritional and respiratory support are required. *Riluzole (Rilutek)*[1] has recently been approved for the treatment of amyotrophic lateral sclerosis but has only a marginal benefit in slowing disease progression. Two different neurotrophic factors are being tested in clinical trials to see if they can slow down the loss of motor neurons.

Juvenile Motor Neuron Disease

This disease, also called monomelic atrophy, begins in young adulthood as a predominantly distal weakness and marked wasting involving one or both upper limbs or one lower limb. Typically, the onset of the disease is insidious and the disease progresses for a few years after which it stabilises. Usually, the motor disability is not as marked as the wasting of muscles. There is no sensory involvement. Unlike amyotrophic lateral sclerosis, there is no involvement of the upper motor neurons or bulbar musculature. Peripheral nerve conduction velocities are normal.

Spinal Muscular Atrophy (SMA)

Spinal muscular atrophy is a hereditary disorder affecting children and young adults and manifesting as lower motor neuron involvement without evidence of upper motor neuron (corticospinal) involvement.

Genetics and classification Genetic studies have shown that there are at least two variants: an autosomal recessive form linked to a gene on chromosome 5 (5q13) and an X-linked variant. Earlier, the classification was based on the age of onset and the rate of progression of the disease, and included four groups: I—congenital (Werdnig-Hoffman) type; II—benign infantile type; III—juvenile (Wolfhart-Kugelberg-Welander) type; IV— adult-onset type.

Congenital SMA

Disease manifestations typically begin in utero as decreased fetal movements. At birth the infant is hypotonic with a weak sucking mechanism (floppy baby syndrome). There are special ways to elicit clinical hypotonia at this age and these are described in detail in pediatric books (scarf sign, lack of development or delay in development of motor milestones). Within a year of birth, the infant dies usually of inanition or respiratory infection.

Benign infantile SMA

The onset is in infancy but the rate of progression is slow and survival upto adulthood may be seen.

[1] Riluzole inhibits glutamate release.

Juvenile SMA

Typically, onset is in the teens as a slowly progressive weakness predominantly affecting the proximal limb girdles. Concomitant distal weakness may be seen. The differential diagnosis is that of proximal weakness (discussed in the approach section). SMA is characterised by prominent muscular wasting, reflex hypotonia, and the involvement of all the muscles at a given myotomal level.

Adult SMA

This condition presents as a proximal muscular weakness and is similar to juvenile SMA except for the age of onset, which is typically in the third decade of life.

Investigations Serum CPK levels are normal or very mildly elevated. The EMG shows a neuropathic pattern and this is confirmed by muscle biopsy.

Treatment Treatment is mainly supportive.

DISEASES OF THE MUSCLE (MYOPATHIES)

Muscle diseases are divided into groups based on what we know about their etiology (Table 9.22). The various groups that will be discussed include muscular dystrophies, congenital myopathies, and metabolic myopathies. The most important criteria for clinical differentiation are the time course of the disease, the presence or absence of a family history, the pattern of muscle weakness and the associated clinical signs and symptoms. All myopathies are symmetrical and muscular fasciculations are absent; normal sensory perception and preserved deep tendon reflexes (till late in the course of the disease) are other additional features that help to differentiate them from other causes of muscle weakness.

Table 9.22 Classification of myopathies

Inherited myopathies	*Acquired myopathies*
muscular dystrophies	inflammatory myopathies
congenital myopathies	toxic myopathies
metabolic myopathies	endocrine myopathies (acquired metabolic myopathies)

Muscular Dystrophy

Muscular dystrophies are inherited myopathies associated with the destruction and regeneration of muscle fibres and their eventual replacement with fibrous and fatty tissue. There is no accumulation of metabolic storage material in the muscle fibres and little, if any, inflammatory activity. It is thought that these diseases are secondary to abnormalities in the complex protein structure responsible for muscular contraction and the integration of the contractile mechanism with the muscle membrane structure. There are a large number of muscular dystrophies. The association between the clinical syndromes and the ultrastructural protein abnormalities is currently being studied.

Clinically, all dystrophies present with progressive, symmetrical muscle weakness. In some dystrophies, the degree of muscle weakness is profound. Such diseases begin early and progress rapidly. Serum CPK levels are very high. The classic example is Duchenne muscular dystrophy. Others have a more indolent course and are associated with moderate elevations of CPK because the rate of muscle destruction is lower.

Duchenne muscular dystrophy (DMD)

This is an X-linked recessive muscular dystrophy defined clinically by childhood onset and rapid progression of muscular weakness; most patients die by the age of twenty years. The abnormal gene is now known to be on the Xp21 band of the X chromosome. It is now known that a similar disease which begins in adolescence and permits survival upto the fourth decade (*Becker dystrophy*) is due to the same genetic mechanism. Hence, both conditions are sometimes called Xp21 myopathies.

Epidemiology The incidence of DMD is approximately 23 per 100,000 live born males. In a third of patients, there is no family history (new mutation).

Genetics and pathophysiology The gene responsible for DMD is the largest human gene identified so far, being 2000 kilobases in size (2 million base pairs). The gene is located on the short arm of the X chromosome. The product of this gene is a large plasma membrane protein called *dystrophin.* The association of dystrophin abnormalities with DMD began with the observation that some carrier females had a translocation at the Xp21 site of the X chromosome. The site was confirmed and its base pair sequence determined and then the gene product was deduced. The identification of dystrophin was one of the first examples of reverse genetics. There are many possible gene abnormalities (point mutations, deletions at different sites) which may result in the complete absence of dystrophin (DMD) or the production of an abnormal dystrophin (Becker's disease). The protein dystrophin acts as a 'strut' to maintain membrane integrity during muscle contraction; in its absence (or insufficiency), the trauma of repetitive contraction results in 'holes' in the sarcolemma. Extracellular calcium enters the muscle fibres and activates destructive enzymes, leading to myocyte necrosis.

Clinical features Typically in DMD, a child starts walking either normally or with a mild delay (18 months). Between the ages of 3 to 5 years, a deterioration in motor capabilities is noted. Initially, there may be frequent falls while running. This is followed by difficulty in climbing stairs, a change in the gait (which becomes waddling), and a difficulty in rising from the squatting posture. The child may hold on to a wall. If no support is available, the child rises by 'climbing up on himself': Gower's sign[1] (Fig 9.27). On examination, pseudohypertrophy

[1] Gower's sign is not specific for DMD and can be seen with any disease causing severe proximal muscle weakness.

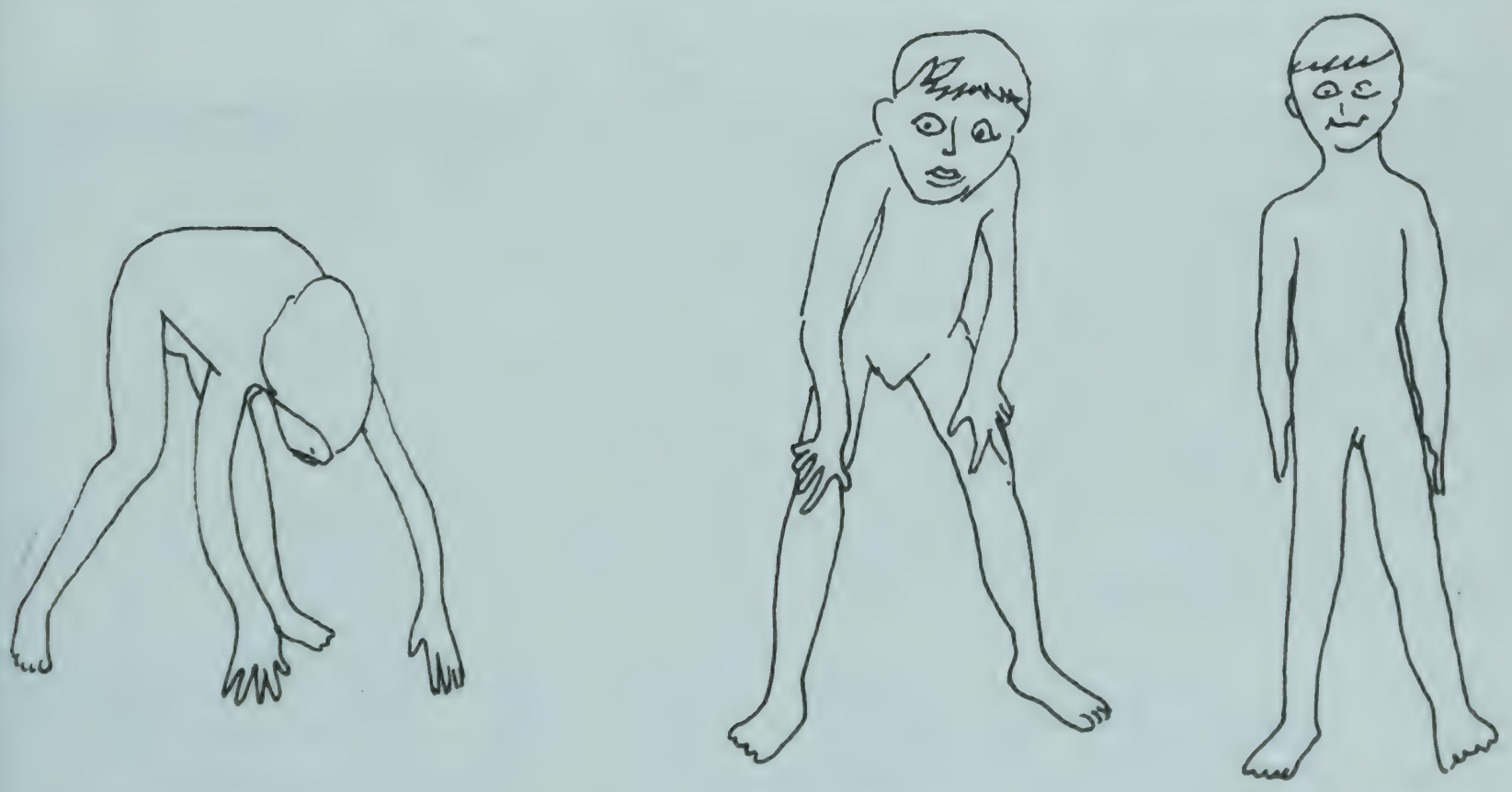


Fig 9.27 Gower's sign

is noted in the calves; it may also be seen in other muscles such as the deltoids and the extensor digitorum brevis in the foot.

Because some muscle groups become weaker earlier than others, the patient develops postural abnormalities and contractures. For example, in the lower limbs the ankle extensors (which are antigravity muscles and are contracting most of the time) weaken before the ankle flexors (the gastrocnemius); hence, the patient walks on his toes and develops contractures of the Achilles tendons. A lordotic posture is assumed to restore the centre of gravity.

The spine may develop scoliosis and this combined with respiratory muscle weakness can lead to respiratory failure; aspiration and pneumonia are the usual causes of death. Other organ involvement in DMD is reflected in a lower mean IQ among patients (85 compared to 100 in normal humans) and cardiac abnormalities.

Investigations The classic three tests for muscle disease, that is, CPK, EMG and muscle biopsy, will confirm the diagnosis of DMD. In DMD, CPK levels are 20–100 times higher than normal. In the very late stage with extensive contractures, the CPK levels may fall. In Becker's dystrophy, CPK levels are 5–10 times normal. Once the diagnosis is clear in one family member, siblings may require only a CPK estimation.

When available, there are two tests that establish the diagnosis of DMD: 1) Immunohistochemistry of the biopsied muscle will show that the membrane either has no dystrophin (DMD) or very little dystrophin (Becker's dystrophy), and 2) DNA analysis of the blood of the patient can identify the abnormal gene and this test can be used for in utero diagnosis as well as for the detection of carriers.

Management Prednisone appears to diminish the rate of progression of DMD. However, there are significant side effects, such as gastrointestinal hemorrhage and weight gain, which can be disabling in a patient with muscle weakness. The role of physiotherapy is controversial but stretching exercises are useful in preventing contractures. In the early stages, a supportive leg brace may be helpful. Subjects with advanced disease usually need a wheelchair and respiratory and nutritional support. Genetic counselling of the parents of affected patients and of carriers is important.

Myotonic Dystrophy

This is an autosomal dominant muscular dystrophy characterised by a typical distribution of muscle weakness, myotonia and involvement of multiple organs.

Epidemiology The incidence is approximately 1 per 8,000. The onset is typically in the teenage years or twenties but the symptoms may begin at birth (congenital myotonic dystrophy) or remain subclinical throughout life.

Genetics and pathophysiology The abnormal gene for myotonic dystrophy is located on the proximal long arm of chromosome 19 (19q13). The gene normally possesses 5 to 35 'repeats' of the triplet codon CTG in the last exon. The normal product of the gene is a protein enzyme called myotonin protein kinase. In the disease, the number of triplet codons increases to over 50. Disease severity is proportional to the number of 'repeats'.

Clinical features Muscle weakness involves the facial musculature, the neck muscles and the distal musculature of the limbs. The face shows ptosis, and atrophy of the masseter and temporalis muscles ('hatchet' facies). Unlike myasthenia gravis, the ptosis in myotonic dystrophy is not accompanied by any weakness of eye closure or extraocular muscles. The associated features include mental retardation, frontal balding, cataracts,[1] hypogonadism, insulin resistance and cardiac abnormalities (conduction defects and diastolic dysfunction).

[1] Posterior subcapsular cataracts

Mothers with mild muscular weakness may have children whose disease begins early. This phenomenon (called anticipation) is due to an increase in the number of triplet codon repeats during the process of oogenesis. Congenital myotonic dystrophy is an extreme example of this. At birth, the infant is hypotonic and shows respiratory distress. If he survives, there will be a delay in motor milestones and mental retardation will be present.

Investigations Serum CPK levels are mildly elevated and the EMG shows myotonia and a 'dystrophic' pattern. On the muscle biopsy, the picture is distinct from most other dystrophies. There is little myocyte necrosis. There are very large muscle fibres with central nuclei. Circular myofibrils wrapped around the longitudinal myofibrils (*ringbenden*) and areas of the sarcoplasm devoid of myofibrils (*sarcoplasmic masses*) are characteristic. DNA analysis permits confirmation of the diagnosis and the detection of carriers.

Management There is no treatment for muscle weakness. Myotonia is rarely disabling; if it is disabling, phenytoin or quinidine are effective agents. The treatment of cardiac conduction defects may be life-saving. Genetic counselling is important.

In general, muscular dystrophy is suggested by a pattern of a slow, steadily progressive illness. There may be a positive family history in parents or siblings. There may be selective sparing or hypertrophy of some muscles which have the same segmental innervation as the other muscles which are affected (a feature unusual in spinal muscular atrophy or polymyositis).

Congenital Myopathies

This term is used for a variety of relatively benign inherited myopathies which are classified based on the microscopic morphology of muscle fibres.

Clinical features Patients show muscle weakness at birth and there may be a mild delay

Table 9.23 Other muscular dystrophies

Disease	*Mode of inheritance*	*Clinical features*
Facio-scapulohumeral dystrophy	AD, gene on chromosome 4	weakness of the face, scapulohumeral and peroneal muscles
Limb-girdle dystrophy	AR/AD	may involve predominantly the pectoral girdle (Erb type), or the pelvic girdle (Leyden-Mobius type); age of onset and pattern of weakness remain similar within families
Scapulo-peroneal dystrophy	AD or X-linked	an X-linked variant with early joint contractures and cardiomyopathy is called the Emery-Dreifuss syndrome
Congenital muscular dystrophy of Fukuyama type	AR	unlike the above three, the onset is in the first year of life and death ensues by age ten; mental retardation, seizures and CT scan abnormalities are prominent

AD = Autosomal dominant, AR = Autosomal recessive

in motor milestones. Muscle development proceeds during childhood although more slowly than in peers. The disease may become manifest at adolescence as the need for physical exertion increases or the patient becomes more aware of his body habitus. Skeletal abnormalities related to the weakness (such as kyphoscoliosis and pes cavus) are common. A few variants may cause feeding difficulties and respiratory problems in infancy.

Investigations Serum CPK levels may be normal or mildly elevated. The EMG shows a myopathic pattern. The muscle biopsy may show single or mutiple *'cores'* (that is, areas devoid of mitochondria) within the muscle fibres, accumulation of Z-disc material (*nemaline bodies* or rods), central nuclei (*myotubule-like*) or a 'disproportion' in the normal ratio of Type I to Type II fibres.

Metabolic Myopathies

Metabolic myopathies may be inherited or may be secondary to an endocrine abnormality. Inherited metabolic myopathies usually interfere with the process of generating energy for muscle contraction. Hence, this group includes glycogen storage diseases, disorders of fatty acid metabolism and inherited disorders of the mitochondria.

Clinical features Metabolic myopathies typically present with limb-girdle weakness. Signs of endocrine abnormalities and organomegaly must be sought. A syndrome of episodic cramps, muscle pain and weakness associated with myoglobinuria is seen in *McArdle's disease* (myophosphorylase deficiency) and *Tarui disease* (phospho-fructokinase deficiency).

Investigations Serum CPK levels are mildly elevated and the EMG shows a myopathic pattern. In hypothyroidism there may be pseudo-myotonia. A careful clinical examination and blood tests for endocrine problems will define the diagnosis in many patients, thereby obviating the need for a muscle biopsy. The blood tests should include thyroid function tests, serum sodium, potassium, calcium and phosphate levels. More specific tests of adrenal and parathyroid function are obtained if clinically indicated.

In the syndrome of episodic cramps with muscle weakness, a *forearm ischemic exercise test* will confirm the diagnosis of a muscle enzyme deficiency.[1] In the inherited metabolic myopathies, a muscle biopsy is useful. There may be glycogen-filled (glycogen storage disease), or lipid-filled vacuoles (lipid storage myopathy) or morphologically abnormal mitochondria[2] (mitochondrial myopathy) in the muscle fibres. The mitochondrial myopathies may also be diagnosed using mitochondrial DNA studies.

INFLAMMATORY DISEASES OF THE MUSCLES

The most common cause of widespread muscle inflammation is autoimmune disease. The other causes are listed in Table 9.24. Three common syndromes have been described. When the disease is confined to the muscles, it is called *polymyositis.* Additional involvement of the skin results in the syndrome of *dermatomyositis.* A third syndrome characterised by the finding of inclusion bodies on microscopic examination of the muscle is termed *inclusion body myositis.* A third of patients with an inflammatory myopathy have an associated collagen vascular disease (rheumatoid arthritis, systemic lupus erythematosus, scleroderma, mixed connective tissue disorder). Ten per cent

[1] A blood pressure cuff is placed above the elbow and inflated to exceed arterial pressure. After 1 minute of vigorous hand exercise, a blood sample is obtained from the antecubital vein. Normally, there is a fourfold increase in blood lactate levels. In Tarui or McArdle's disease, blood lactate levels do not rise.

[2] In mitochondrial myopathies, the muscle fibres look 'ragged and red' under the light microscope and using a special stain (Trichrome-Gomori). Electron microscopy shows a mitochondria of abnormal size and shape.

of patients, more commonly older patients with dermatomyositis, have an underlying malignancy.

Table 9.24 Causes of inflammatory myopathies

1. **Idiopathic**
   - Polymyositis
   - Dermatomyositis
   - Inclusion body myositis
   - Polymyalgia rheumatica
2. **Infection/Infestation**
   - Bacterial
     - Tropical pyomyositis
   - Viral
     - Picorna virus
     - Coxsackie
     - HIV
   - Parasitic
     - Cysticercosis
     - Trichinosis
     - Toxoplasmosis

Epidemiology Polymyositis typically affects young adult females. Dermatomyositis affects children and adults equally. The estimated annual incidence of inflammatory myopathies is about one per 10,000–20,000.

Clinical features Patients present with subacute symmetrical weakness of the proximal limb musculature and neck muscles. The onset may be preceded by a brief, febrile illness. About a fifth of patients experience moderate to severe muscle pain. There may be dysphagia, dysphonia and rarely, respiratory impairment. A third of the patients may have myocardial involvement (myocarditis). The ocular and facial muscles are usually spared. Sensory examination is normal. Deep tendon reflexes may be normal or diminished. Reflexes are rarely absent unless muscular weakness is extreme; absent reflexes raise the possibility of the Guillain-Barre syndrome.

In dermatomyositis, the pattern of muscle weakness is the same but in addition there are characteristic skin changes. There is periorbital edema and a purplish discolouration of the skin over the eyelids and cheeks (*heliotrope rash*). Papular thickening of the skin may be seen over the proximal interphalangeal joints, elbows and knees (*Gottron's patches*). Abnormalities of nail-fold capillaries may be seen. Ectopic calcification may occur usually in the subcutaneous tissues and sometimes in the muscle.

Pathology and pathophysiology In polymyositis, the muscle biopsy shows numerous necrotic muscle fibres, and degenerating and regenerating myofibres. Necrotic myofibres appear hypereosinophilic and have lost their nuclei. Regenerating myofibres look small, rounded, basophilic and have central nuclei. There is extensive lymphocytic infiltration of the muscles and phagocytosis of necrotic muscle cells may be present. The lymphocytes appear to be mostly T cells of the cytotoxic variety.

In dermatomyositis the muscle biopsy looks very different and the pathogenesis is also different. There is deposition of circulating immune complexes and complement in the walls of the intramuscular arteries and veins. This vasculitis is associated with endothelial hyperplasia and areas of infarcted muscle. Perifascicular atrophy is characteristic of dermatomyositis. Within each fascicle the central muscle fibres are relatively preserved but the peripheral ones become atrophic.

Diagnosis The development of muscle weakness in polymyositis is usually more rapid than that seen in other myopathies. Once the diagnosis of polymyositis is suspected based on the clinical picture, the diagnosis may be confirmed in three sequential steps: muscle enzymes are initially obtained followed by an electromyographic study.[1] Finally a muscle

[1] Doing an EMG or even administering an intramuscular injection can result in a spurious elevation of serum CPK levels for 48–72 hours.

biopsy can prove the diagnosis. CPK levels are markedly elevated. Transaminases, aldolase and lactate dehydrogenase will also be elevated but need not be measured in all cases. The EMG shows a myopathic pattern but may show a neuropathic pattern in some areas. There are signs of muscle irritability, such as, increased insertional activity, fibrillations and repetitive discharges. Supportive investigations include an elevated ESR (seen in 50 per cent of subjects) and a variety of antinuclear antibodies called the *anti-Jo-1 antibody.*[1]

Differential diagnosis An asymmetric weakness, altered sensation or cranial nerve abnormalities should suggest an alternative diagnosis. Endocrine myopathies can mimic polymyositis.

Hyperthyroidism, hypothyroidism, hyperparathyroidism, Cushing's disease, primary aldosteronism, Addison's disease and diabetic amyotrophy should all be considered in the differential diagnosis. Metabolic myopathies (McArdle's disease, carnitine deficiency) can mimic polymyositis but the urine may show myoglobin.

The infectious causes of myositis include toxoplasmosis, trichinosis and HIV infection. Some drugs and toxins (alcohol, chloroquine, d-penicillamine and zidovudine) can also cause myositis.

Therapy Corticosteroids are the mainstay of therapy. Prednisone is usually started at 40 to 60 mg/day, (potassium supplements, antacids or histamine type 2 receptor blockers, and calcium supplements may be administered concurrently to avoid some of the side effects of the steroid therapy) and after several months is gradually reduced as muscle strength improves and CPK levels fall. Maintenance doses of steroids may need to be continued for several years. A few patients may develop worsening of weakness while on steroids; the cause may be refractory disease or a steroid-induced myopathy. CPK levels are useful in differentiating between these two conditions, being higher in refractory disease.[2] In acute, severe polymyositis, bolus intravenous methylprednisolone may be effective.

Patients who either do not respond to steroids or cannot tolerate it, may respond to azathioprine (Imuran), cyclophosphamide, methotrexate, cyclosporine or infusions of intravenous immunoglobulin (IgG). Malignancy-associated myositis may remit with tumour removal.

Inclusion Body Myositis

This condition is a variant of inflammatory myopathy occurring in older patients and presents with lower limb proximal weakness. Fifty per cent of patients may also have wasting and weakness of distal muscles. The muscle biopsy shows distinctive cytoplasmic and nuclear inclusions. Each inclusion is a vacuole with regularly arranged filaments within. The disease does not respond to glucocorticoids.

Myasthenia Gravis

Myasthenia gravis is a disorder of neuromuscular transmission characterised clinically by fluctuating weakness due to easy fatiguability of the commonly used voluntary muscles. Typically, the cranial musculature is affected early producing symptoms such as diplopia, ptosis and difficulty in swallowing.

Epidemiology It is estimated that the incidence of myasthenia gravis is 1 per 20,000. The disorder typically occurs in adulthood and has a bimodal age- and sex-distribution. Younger patients (more often women) are in the third or fourth decade of life and in them the disease may sometimes be associated with other autoimmune disorders. Older patients (more often men) are typically in the seventh decade and in them, the

[1] Anti-Jo-1 antibody is an antibody to the enzyme histidyl-tRNA synthetase.

[2] In steroid myopathy EMG will not show increased insertional activity and fibrillation potentials. Muscle biopsy will not show active inflammation. A trial period off steroids will result in the improvement of clinical weakness.

disease may be associated with a malignancy elsewhere. Hyperthyroidism may be seen in 5 per cent of the patients. At any age most patients have idiopathic myasthenia gravis without any associated illness. Overall, women are affected slightly more often than men (F:M=3:2).

Pathogenesis Myasthenia gravis results from a failure of normal transmission across the neuromuscular junction. There is a reduction in the number of acetylcholine receptors on the postjunctional muscle membrane. Myasthenic patients develop specific antibodies to the acetylcholine receptors on the postjunctional muscle membrane. These autoantibodies bind to the receptor and appear to impair neuromuscular transmission by at least three mechanisms: they block the receptors functionally, bring about an accelerated degradation of the receptors, and bind circulating complement to damage these receptors by complement-mediated lysis. Additionally, cellular immune activity against the acetylcholine receptor has also been documented. What initiates this autoimmune response is still not clear. The thymus has been a candidate for the source of this autoimmune response as thymic abnormalities have been noted in 75 per cent of patients (hyperplasia in 85%, thymoma in 15%). Furthermore, thymectomy results in clinical improvement in most patients. It has been suggested that the thymus has myoid cells which have an acetylcholine receptor; an immune response against the acetylcholine receptors on these myoid cells may be a central event in myasthenia gravis. Genetic factors may also increase the likelihood of myasthenia gravis; a moderate association has been noted with HLA antigens B8 and DRw3.

Clinical features Myasthenia gravis usually has an insidious onset. The most common symptoms of myasthenia gravis are development of ptosis, diplopia and muscle fatiguability after exercise. Very characteristically, muscle fatiguability recovers after a period of rest. As a result, the patient typically feels well in the morning after a night's rest and develops symptoms as the day progresses. Ocular muscles are affected initially in about 40 per cent and eventually in the majority of patients. The facial muscles, bulbar muscles and proximal limb muscles soon become involved, although the muscular weakness may remain localised to the ocular muscles in 15 per cent (*ocular myasthenia*). Involvement of bulbar muscles is characterised by the onset of dysphagia, dysarthria, a nasal quality to speech (which also becomes reduced in volume after prolonged talking) and nasal regurgitation. The face appears relatively expressionless. When the patient tries to smile, the corners of the mouth do not move upwards resulting in a grimace (described as a *myasthenic snarl*). Weakness of jaw muscles can cause a 'hanging jaw' and difficulty in chewing. Weakness of extensor muscles of the neck can result in a slight forward drooping of the head. Weakness of the limb muscles is usually more marked proximally rather than distally and manifests as a difficulty in lifting weights, climbing stairs or walking long distances. It is not as prominent as the weakness of ocular and bulbar muscles. The involvement of the diaphragm and thoracic respiratory muscles can result in life-threatening respiratory embarrassment. Unrelated infections, sudden withdrawal of treatment or a systemic illness can precipitate an acute exacerbation of the muscle weakness requiring nasogastric intubation (in case of swallowing difficulty) and respiratory assistance. The patient is said to be *in crisis*.

Findings on the physical examination reveal a pure motor weakness without loss of sensations or deep tendon reflexes. Pupillary responses are normal. The diagnosis is strongly supported by the demonstration that muscular weakness accompanies repetitive or sustained contraction and improves after a period of rest. The most

useful quantitative tests include a 'single breath count', 'timed forward arm abduction' or 'timed eyelid elevation',[1] vital capacity and dynamometry of selected muscles.[2] If the trunk and limb muscles are involved, the patient can be asked to perform repetitive movements such as arm flaps, 'sit-ups' or 'jumping jacks'; the number of movements performed before fatigue, is counted. These tests are useful to assess temporal variation in a given patient. The tests may be repeated half an hour after a dose of neostigmine and just before the next dose to assess the peak and trough response to medication. They are less useful in comparing the disease severity between different patients.

Diagnosis Confirmation of the clinical diagnosis can be achieved with laboratory tests which should be performed in the following order: the edrophonium (*Tensilon*) test, EMG with repetitive nerve stimulation, anticholinesterase antibody assay and single fibre EMG (if necessary). Edrophonium is a short-acting cholinesterase inhibitor. In the Tensilon test, a baseline testing of muscle power and fatiguability is performed and recorded. Edrophonium is then injected (2 mg initial test dose followed by 8 mg after 30 seconds if the patient tolerates the initial bolus). Myasthenic patients demonstrate a characteristic improvement in muscle strength that begins within 30–60 seconds and lasts for about 5 minutes. The test should be performed with the availability of atropine and respiratory support facilities as severe respiratory depression can occur on occasion. If 'functional' weakness is suspected and the patient claims a dramatic improvement after Tensilon injection, it may be desirable to perform a blinded comparison of edrophonium versus an injection of saline. Occasionally, patients with pure ocular myasthenia may not show a response to the Tensilon test; an oral dose of neostigmine may, however, relieve symptoms or signs in half an hour. In *repetitive nerve stimulation,* the voltage of the muscle action potential is measured during repetitive, low frequency stimulation of the motor nerve (two to five stimuli a second). A rapid reduction in the amplitude of the evoked muscle action potential (*decremental response* of 15 per cent) is considered a positive response; in normal subjects, there is no significant change in voltage. This test is positive in the proximal muscles in about 80 per cent of myasthenics. Assays for serum antibodies to acetylcholine receptors are not routinely available in our country; when performed, antibodies are found to be present in the serum of about 85 per cent of patients with generalised myasthenia and in about 60 per cent of patients with ocular myasthenia.

The *single-fibre EMG* detects delayed or failed neuromuscular transmission in pairs of muscle fibres supplied by a single nerve fibre and increases the diagnostic yield to over 95 per cent. The abnormal finding is described as an *increased jitter.*

A routine chest X-ray (posteroanterior and lateral) should be obtained in all patients with myasthenia gravis. Such a plain film will detect most if not all macroscopic thymomas. Although a CT scan of the mediastinum improves the detection rate of thymomas, false positive scans are fairly common. A CT scan should not be performed routinely on all myasthenics but is usually done preoperatively (before thymectomy).

Treatment Four treatment modalities are used for treating myasthenia gravis: enhancement of neuromuscular transmission with anticholinesterase drugs, surgical thymectomy, long term immunosuppression and short term immunosuppression (with plasmapheresis or intravenous gammaglobulins).

Neostigmine (15–60 mg oral q 3–4 hours) and pyridostigmine (60–240 mg oral q 3–8 hours) are

[1] The patient is asked to hold out her arms or to look up and maintain this position as long as possible. Eyelid elevation can usually be sustained for a minute, or more.

[2] A rolled sphygmomanometer cuff may be used to provide a rough estimate of grip strength if a hand dynamometer is not available.

the principal anticholinesterases.[1] The frequency and timing of doses are decided by the patient's symptoms. When parenteral therapy is required (in myasthenic crises), neostigmine 0.5 mg i.v. or 1.5 mg i.m. may be used instead of a 15 mg dose; for pyrido-stigmine 2 mg i.v/i.m is equivalent to a 60 mg oral dose. These drugs increase the concentration of acetylcholine at the neuromuscular junction by inhibiting its degradation. These drugs result in muscarinic side effects, such as sweating, salivation, abdominal cramps, and diarrhea. A long acting preparation may be given at bedtime so that swallowing is not difficult in the morning.

Pyridostigmine has a lower incidence of autonomic side effects compared to neostigmine. It is important to educate patients about the illness, the effects of the drugs used and the possibility of acute worsening of muscular weakness that may result from both undertreatment and overtreatment.

Severe muscular weakness in a myasthenic being treated with an anticholinesterase, may be due to acetylcholine build-up at the neuromuscular junction (resulting in excess depolarisation of muscle known as *cholinergic crisis*) or may be the result of a lack of acetylcholine at the neuromuscular junction (*myasthenic crisis*). These two conditions must be distinguished. Increased weakness at the time of peak drug effect, and the presence of muscarinic side effects (excessive sweating and salivation, gastrointestinal distress, miotic pupils, and bradycardia) suggest a cholinergic crisis. The omission of a drug dose, wearing away of its peak effect and an improvement with intravenous edrophonium suggest a myasthenic crisis.

Patients with mild disease (or pure ocular myasthenia) may be treated initially with anticholinesterase drugs. Sometimes these drugs may not relieve extraocular muscle weakness. Ephedrine (25 mg t.i.d. or q.i.d.) may then be tried as an adjunct.

Thymectomy is indicated in most myasthenic patients below 60 years who have generalised disease and who are symptomatic despite the use of anticholinergic agents. Thymectomy is also indicated if a thymoma is demonstrable. Most patients improve after thymectomy, require lower doses of medication and a third may achieve drug-free remission. The benefit of thymectomy may not appear immediately after surgery but may be seen over the next few months to years. Because there may be perioperative worsening, thymectomy should only be carried out in a hospital with facilities for intensive care and respiratory support.

The patients who do not respond to anticholinesterases or who are not good candidates for surgery (in case they are above 60 years of age), can be given a trial of immunosuppressive therapy. Prednisone (60 mg on alternate days), azathioprine (2–3 mg/kg/d) and cyclosporin (5 mg/kg/d in 2 divided doses) have all been used with similar degrees of success. Prednisone is the most frequently used agent. It can precipitate a transient worsening and, therefore, therapy is best initiated in a supervised setting or by starting with a low dose. Cost and toxicity render the use of long term cyclosporin less attractive.

Short term immunosuppression is used for myasthenic patients who are seriously ill and have failed to respond to any of the above programmes or are awaiting thymectomy, and in patients with refractory myasthenic crisis requiring ventilatory assistance. Plasmapheresis (five exchange treatments of 3–4 litres each over a two week period) or intravenous gamma globulin (400 mg/kg/day for 5 days) are the two options. Both the options provide good short term relief.

Myasthenic (Eaton-Lambert) Syndrome

The myasthenic syndrome, or Eaton-Lambert syndrome, is a rare myasthenia-like disorder resulting from an impaired release of acetylcholine from the presynaptic membrane. The limbs are predominantly affected and the ocular and bulbar muscles are typically spared. The disorder occurs more often in elderly men

[1] One tablet of pyridostigmine is roughly equivalent to one tablet of neostigmine.

and is associated with intrathoracic tumours (70 per cent have small-cell lung cancer). Unlike myasthenia, muscle power increases on repetitive or sustained contraction, deep tendon reflexes may be lost, and repetitive nerve stimulation results in an increase in muscle action potential (*incremental response*). Besides treatment of the underlying malignancy, prednisone and guanidine hydrochloride (25–50 mg/kg/day in divided doses) have been found to be helpful.

Periodic Paralyses

Periodic paralyses are characterised by attacks of muscle weakness associated with changes in the levels of serum potassium (Table 9.25).

Table 9.25 Classification of periodic paralyses

Primary	*Secondary*
1. Hypokalemic	1. Hypokalemic
2. Hyperkalemic	thyrotoxic
with myotonia	diuretic abuse/urinary potassium loss
with paramyotonia	gastrointestinal potassium loss
3. Normokalemic	barium intoxication
	2. Hyperkalemic
	renal insufficiency
	adrenal insufficiency

General clinical features In *primary* periodic paralysis, although the serum potassium increases or decreases from the basal level, it may remain within normal limits during the attack. In *secondary* periodic paralysis, the serum potassium level is below 3 mEq/L or above 7 mEq/L. At these levels, the abnormal serum potassium can cause serious cardiac arrhythmias.

The different types of periodic paralyses share some common clinical features. The attacks may last from less than an hour to up to four days. The muscular weakness may be focal or generalised and tendon reflexes diminished during attacks. If the weakness is generalised, proximal muscles of the limb are the first to be affected. Complete recovery between attacks is usual but with repeated attacks there may be a permanent weakness associated with a vacuolar myopathy.

Primary hypokalemic periodic paralysis

Primary hypokalemic periodic paralysis is transmitted as an autosomal dominant trait, but a third of the cases arise sporadically. The pathogenetic feature appears to be an abnormality in a particular type of calcium channel protein, the gene for which is located on chromosome 1 (1q31). Men are clinically symptomatic more often than women and the first attack is usually in adolescence. The frequency of the attacks decreases in middle age. Attacks are precipitated by prolonged rest after exercise, or with the ingestion of a large carbohydrate meal. The diagnosis is made based on the history and the response of muscle weakness to potassium replacement. In patients with a low frequency of attacks, the diagnosis may be established between attacks using a provocative test in which glucose and insulin are administered simultaneously (to induce hypokalemia). The diagnosis is confirmed if weakness is demonstrated in parallel with the fall in serum potassium levels. Such a test is potentially hazardous and the patient should be carefully monitored during and after the test for 24 hours.

Treatment of an acute attack consists of oral potassium supplementation in the form of syrup potassium chloride at a dose of 0.3 mMol/kg, repeated every 15 to 30 minutes. The response to potassium supplementation is assessed using serial ECG tracings, testing muscle strength and by hourly serum potassium estimation. Milder attacks may resolve spontaneously. If the oral potassium causes gastrointestinal distress, or if the patient is unable to swallow, or if the serum potassium is below 3 mEq/L, intravenous potassium chloride is administered diluted in mannitol. Administration of potassium in

5 per cent glucose may worsen the condition. For the prevention of attacks, ingestion of smaller, more frequent meals and regular exercise as well as avoiding unusually severe exercise may be sufficient. If not, acetazolamide or a potassium-sparing diuretic may be used to prevent attacks. Chronic potassium supplementation is not helpful in preventing attacks.

Hyperkalemic periodic paralysis

This disorder is inherited as an autosomal dominant trait. A mutation in the adult skeletal muscle sodium channel gene located on chromosome 17 (17q23) appears to be the genetic basis of this disease.

In this condition, attacks of muscular weakness begin before the age of 10 years and may be precipitated by fasting or rest after exercise. The patient may show myotonia or *paramyotonia*.[1] The administration of potassium worsens the muscular weakness and oral glucose hastens recovery. Thiazide diuretics are effective in preventing recurrent attacks.

Peripheral Neuropathy

Peripheral neuropathies are disorders affecting the peripheral nerves. This term is sometimes used as a synonym for *polyneuropathy,* that is, a widespread involvement of the peripheral nerves. Other syndromes which are also diseases involving parts of the peripheral nervous system but have distinct names include *radiculopathy* (disease of the spinal roots), *plexopathy* (disease of the spinal nerve plexuses), *mononeuropathy* (involvement of a single nerve), *mononeuritis multiplex* (involvement of two or more individual nerves) and *reflex sympathetic dystrophy* (involving the autonomic fibres).

Diseases of the peripheral nervous system may be attributed to a large variety of causes and in 25 per cent of cases the cause may not be clear even after a detailed evaluation. We will discuss the peripheral neuropathies first as syndromes and then according to etiology.

Principal neuropathic syndromes

Neuropathic syndromes are defined based on the time course of the disease, and based on the type (motor, sensory or both), and pattern of involvement (proximal, distal or focal). The electromyogram (EMG) may be useful in further defining whether the involvement is predominantly axonal or demyelinating, and in confirming the clinical localisation.

1. *Syndrome of acute motor paralysis with variable sensory and autonomic involvement*

The classic syndrome is *Landry-Guillain-Barre* (LGB) syndrome. Other peripheral neuropathies presenting in this pattern include variants of LGB syndrome (such as, acute motor axonal neuropathy [AMAN], a syndrome following certain infections (infections mononucleosis, HIV infection, viral hepatitis, diptheria), acute uremic polyneuropathy, porphyric polyneuropathy, toxic (tri-ortho-cresyl phosphate and other organophosphates, thallium], and postvaccinal [BPL rabies vaccine]). Rarely an LGB-like syndrome may be seen in patients with lymphomas or following renal transplantation.

2. *Syndrome of subacute symmetrical sensori-motor paralysis*

These neuropathies evolve over several weeks, are typically axonal and often manifest with prominent paresthesia. This syndrome is typically due to a metabolic factor which may be a *nutritional deficiency state, or an intoxication.*

3. *Syndrome of subacute and asymmetrical neuropathy*

This syndrome is often a result of the summation of deficits due to multiple mononeuropathies (mononeuritis multiplex). The individual deficits may manifest in nerves far from each other and at different times. The causes of this syndrome are *immuno-inflammatory* or *vascular* diseases. Diabetes mellitus-related neuropathy may present in this fashion. *Predominantly motor* involvement is

[1] Classically myotonia is more severe in the first contraction after a period of rest. In paramyotonia, myotonia worsens with repeated contraction.

seen in severe systemic necrotising vasculitis (polyarteritis nodosa), Churg-Strauss syndrome, rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis and Wegener's granulomatosis. In all these conditions, nerve involvement is secondary to a vasculitis of the vasa nervorum. *Predominantly sensory* involvement is seen in Sjogren's disease.

Other causes of this syndrome include sarcoidosis and Lyme disease. All the above causes show a predominantly axonal pattern on the EMG. A predominantly demyelinating mononeuritis multiplex is called *multifocal motor neuropathy* (MMN).

4. *Syndrome of chronic polyneuropathy progressing over months*

A chronic peripheral neuropathy progressing over months in a patient without a positive family history is usually axonal; such an axonal neuropathy may be secondary to a systemic illness (diabetes mellitus, connective tissue diseases, uremia, hypothyroidism), malignancy (paraneoplastic syndromes) or a toxin (organic solvents). Other causes include leprosy and amyloidosis.[1] Upto a third of elderly patients may have a very mild, non-progressive, peripheral neuropathy of this type but the diagnosis should only be made after excluding treatable causes. A chronic polyneuropathy with a demyelinating pattern on the EMG is secondary to a paraproteinemia or, rarely, Hodgkin's disease.

5. *Syndrome of chronic polyneuropathy progressing over years*

The cause of this syndrome is almost always genetically determined. A family history should be sought very carefully. Examination of available family members may confirm the diagnosis even if a positive family history is not forthcoming.

6. *Recurrent or relapsing polyneuropathy*

The most common cause is *chronic inflammatory demyelinating polyneuropathy* (CIDP). Recurrent attacks of acute intermittent porphyria or repeated exposures to a toxin (such as arsenic) may present as a relapsing polyneuropathy. Mononeuritis multiplex may progress in a stuttering fashion. Metabolic causes include Refsum's disease and Tangier's disease.

7. *Plexopathies*
8. *Mononeuropathies*

Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP, Landry-Guillain-Barre Syndrome)

AIDP is an acute immunoinflammatory predominantly demyelinating peripheral nerve disease which presents as an ascending paralysis.

Epidemiology AIDP occurs in all age and sex groups and the incidence worldwide is approximately 1 per 60,000. An association of the illness with antecedent infection by *Campylobacter jejuni* has been reported. An AIDP-like syndrome has also been associated with Hodgkin's disease, HIV infection and a reaction to certain vaccines.

Clinical features The major clinical manifestation of AIDP is motor weakness which evolves over 3 to 15 days (in rare cases over 4 weeks). Weakness begins typically in the proximal muscles of the lower limbs and proceeds in a more or less symmetrical fashion to involve the distal musculature of the lower limbs, the upper limbs first proximally and then distally, the trunk, muscles of respiration, neck, and rarely, the cranial musculature. The onset of the illness is preceded by a mild upper respiratory or gastrointestinal syndrome in two-thirds of patients. The weakness may be associated with an aching pain and tingling paresthesiae in the affected limbs. However, sensory impairment is rare, and when present, tends to affect vibration before touch. There is early diminution of deep tendon reflexes which rapidly proceeds to areflexia. Hypotonia is noted but there is no muscular atrophy.

[1] These two conditions, along with diabetes mellitus, are the three major causes of predominant *small fibre pattern* of sensory loss (Group C fibres affected).

The two most dangerous manifestations of this illness are paralysis of the respiratory muscles and disturbances of autonomic function. Rapid progression of weakness, involvement of the upper limbs, tachypnea, reduced chest expansion and a reduced single breath count[1] are warning signs of possible progression to respiratory insufficiency.

Autonomic dysfunction can manifest as cardiac arrhythmias, marked fluctuations of blood pressure and profuse sweating. Urinary retention is rare, occurring in about 10 per cent.

A variant of AIDP is characterised by onset with ophthalmoplegia, sensory ataxia and areflexia (*Fisher's variant*).

Pathogenesis The pathogenesis of AIDP appears to be a T cell-mediated immune attack on a constituent of the peripheral nerve myelin sheath. Studies using an animal model of AIDP (called *experimental allergic neuritis* or EAN) suggest that this antigen is a basic protein called P_2.

Pathology The disease affects the ventral nerve roots of spinal and cranial nerves and can later extend to affect the entire length of the nerve. Lymphocytic infiltrates and patchy demyelination are characteristic, with relative sparing of the axons.

Differential diagnosis The conditions to be considered in the differential diagnosis of a subject with rapid acute ascending paralysis are as follows:

Differential diagnosis of rapid acute ascending paralysis

1. Poliomyelitis
2. Acute myasthenia gravis
3. Botulism
4. Snake bite
5. Tick paralysis
6. Shellfish poisoning

[1] The patient is asked to take a deep breath and count while exhaling. The count reached before the patient has to stop for taking her next inhalation is a single breath count. Typically, a patient counting at the rate of 1 per second can reach up to 50.

Cervical cord lesions, atlantoaxial dislocation and basilar artery thrombosis can present with quadriparesis and the patient may be areflexic during the initial stage of spinal shock. However, plantar responses are extensor, sensory signs and bladder involvement may be present, and in a brainstem stroke there is usually altered sensorium.

Investigations A lumbar puncture is not essential to make a diagnosis of AIDP but may be useful. The CSF is under normal pressure and is acellular (or contains only a few lymphocytes) but typically the protein content is high (probably due to inflammation of the nerve roots). The picture of high protein content with few cells in the CSF is called *albuminocytologic dissociation.* The diagnosis is confirmed on nerve conduction studies, best performed a few days after the onset of symptoms. A demyelinating pattern with conduction blocks is seen.

Treatment Management consists of supporting the respiration and circulation until the patient spontaneously improves. Patients with Guillain-Barre syndrome who present acutely should be referred to a centre with intensive care facilities, if this is possible. Immunosuppressants may hasten recovery. Oral steroids were initially used but have been shown to be ineffective. Plasmapheresis (200 ml/kg exchanged over 4 to 5 days daily or on alternate days) is performed if the patient appears to be progressing, cannot walk, has bulbar weakness or has a vital capacity below 20 ml/kg. Complications of the procedure include hypotension, arrhythmias, and bleeding; the procedure must be done in specialised centres. High-dose intravenous immunoglobulins (0.4 g/kg for 5 days) are safer and as effective, but extremely expensive.

The need for respiratory support is best evaluated using regular bedside estimation of forced vital capacity as well as arterial blood gas analyses. Where this is not possible, the clinical indicators have been discussed earlier. The normal vital capacity is over 65 ml/kg. Below a

value of 30 ml/kg, there is a poor cough and secretions accumulate; hence, chest physiotherapy is advisable. The patient should also be reminded to take a deep 'sighing' respiration several times each hour. This prevents pulmonary atelectasis. When the vital capacity decreases to less than 20 ml/kg, the patient can no longer sigh and elective intubation and intermittent positive pressure ventilation may be used to prevent atelectasis and postpone respiratory fatigue. Full respiratory support is required if vital capacity values fall below 10 ml/kg.

Variants of AIDP

A syndrome clinically similar to Guillain-Barre syndrome but associated with axonal degeneration (rather than demyelination) has been described in many children in China. This has been called *acute motor axonal neuropathy (AMAN)*. Pathological studies show that it is mediated by an autoimmune attack on the inner surface of the myelin sheath.

Some patients who recover from AIDP may later develop relapses or a chronic progressive sensorimotor demyelinating neuropathy. If the progression continues for more than 2 months, a diagnosis of *chronic inflammatory demyelinating polyneuropathy* (CIDP) is made. The cranial nerves and autonomic nervous system are not involved. Deep tendon reflexes are diminished or absent, peripheral nerves may be palpably thickened and many patients may have papilledema due to a raised CSF protein which interferes with CSF flow. The EMG shows a demyelinating pattern in both the motor and the sensory nerves with conduction blocks. The pathophysiology is thought to be a delayed type of hypersensitivity response. Repeated demyelination and remyelination can cause onion-bulb formation (of nerves) and secondary axonal degeneration. Other causes of a demyelinating polyneuropathy (hereditary, paraproteinemia) should be excluded. The treatment consists of 6–8 week courses of oral steroids (prednisone 60 mg/d), and, if required, other immunosuppressant.

A recently described entity (*multifocal motor neuropathy* (MMN)) can resemble CIDP or amyotrophic lateral sclerosis. There is involvement of only the motor nerves resulting in prominent wasting, and normal or brisk deep tendon reflexes. Nerve conduction studies show normal sensory nerve conduction but the

Table 9.26 Nutritional neuropathies

Etiologic factor	*Clinical characteristics*
Thiamine deficiency (beriberi)	prominent pain and muscle cramps; alcoholics vulnerable; cardiac failure and stasis pigmentation may be seen
Niacin deficiency (pellagra)	associated diarrhea and dementia; myelopathic features may be seen
Strachan syndrome (Jamaican neuritis)*	predominantly large fibre neuropathy; associated visual impairment, deafness, dizziness and orogenital dermatitis
B_{12} deficiency (subacute combined degeneration)	myeloneuropathy; spasticity, absent ankle jerk with upgoing plantar response
Pantothenic acid	dysesthesiae are prominent
Pyridoxine deficiency	may be precipitated by INH or hydralazine treatment
Vitamin E deficiency	associated cerebellar ataxia

* *Strachan syndrome* may be a toxic neuropathy due to a mycotoxin in fungus-infected sugarcane.

evidence of demyelination in many motor nerves. Many patients have a circulating antibody to GM ganglioside. Treatment is with plasmapheresis or with intravenous immunoglobulin.

Toxic and Metabolic Neuropathies

The prototype of a polyneuropathy is seen in this subset of patients. The classic pattern will be described and individual variation in the different conditions will then be highlighted. The longest axons are the first to be affected since the distal portion of the axon depends on proteins synthesised in the neuronal soma and transported distally. This process of axonal transport is impaired in the toxic-metabolic neuropathies. The first symptoms are sensory paresthesiae in the feet followed by the simultaneous onset of objective sensory and motor findings. If paresthesiae are severe, the patient may pace in an attempt to relieve the symptoms ('burning foot' or 'restless leg' syndrome). Sensory impairment begins in the sole of the foot and proceeds in a 'stocking' fashion. As the area affected progressively enlarges, the originally affected areas show increasing sensory impairment. By the time the sensory impairment has reached the upper shin, paresthesiae begin in the fingertips and by the time it has reached the midthigh, a triangular area of hypesthesia may be demonstrated on the lower abdominal wall. The area grows broader as the apex extends rostrally. The weakness is first demonstrable in the dorsiflexion of the great toe and motor weakness also extends in a graded, symmetric, distal to proximal progression. Typically, the extensor and abductor muscles are affected more severely than those mediating flexion and adduction. Foot drop may be seen. Deep tendon reflexes are diminished and are lost early in the disease, the ankle jerks being the first to go.[1]

1 Reflexes may remain intact if only the small sensory nerve fibres are affected leaving the reflex arc (that is, proprioceptive afferents and motor efferents) intact.

Metabolic Neuropathies

Diabetes mellitus, nutritional deficiencies and malignant cachexia can commonly cause a polyneuropathy. Malignancies (myeloma, lymphoma, lung cancer), liver failure and uremia are the other important systemic diseases resulting in a polyneuropathy. Rare causes include hypoglycemia, hypothyroidism, primary biliary cirrhosis, polycythemia vera, porphyria and amyloidosis. Diabetic neuropathy has been discussed in the endocrine section. Nutritional neuropathies are discussed in Table 9.26 and paraneoplastic syndromes in a separate chapter.

Drug-induced polyneuropathy

A pure sensory neuropathy may be seen with the following drugs: cis-platinum (associated hearing loss is a clue), metronidazole, and high dose pyridoxine. A predominantly sensory neuropathy with a variable degree of motor involvement may be seen with vincristine, thalidomide, phenytoin and hydralazine. A mixed sensorimotor pattern is seen with isoniazid, nitrofurantoin, gold and amiodarone. A pure motor neuropathy may occur with dapsone.

Toxic Neuropathies

Uremic polyneuropathy is related to dialysable toxins of a molecular weight intermediate between that of urea and albumin (middle molecules). Successful renal transplantation can reverse a polyneuropathy. Exogenous toxins causing neuropathy include lead (predominantly motor), acrylamide (predominantly sensory large fibre type), and DMPN[2] (predominantly sensory 'small fibre' type). Other toxins cause a sensorimotor neuropathy; these include organophosphorus, thallium (from rat poisons), arsenic, carbon disulphide and industrial solvents (such as N-hexane). At the onset there may be very painful paresthesiae.

2 DMPN: dimethylaminopropionitrile

Table 9.27 Hereditary neuropathies secondary to inherited metabolic diseases

Pattern of neuropathy	*Underlying disorder*	*Inheritance*	*Metabolic defect*	*Clinical features involved*	*Other systems*
Dorsal root ganglions affected:	Fabry's disease	X-linked recessive	accumulation of ceramide trihexoside	painful, sensory neuropathy ('small fibre' type)	kidney, skin (cutaneous angiofibroma), lung
Neuronopathy	Abetalipoproteinemia	AR	absence of apolipoprotein B	marked proprioceptive disturbance	acanthocytosis, retinitis pigmentosa
	Amyloidosis (hereditary)	AD	mutation in prealbumin gene (transthyretin); chromosome 18	'small fibre type' sensory neuropathy, autonomic neuropathy; diagnosis by blood test for TTR-MET 30 polypeptide or presence of amyloid in nerve biopsy	corneal abnormalities in some families
Axonal					
	Porphyria (acute intermittent, variegate, and erythropoietic)	AD	enzyme defects in porphyrin pathway	recurrent attacks of proximal motor weakness	skin lesions may occur (VP/EP), photosensitivity, dark coloured urine during attacks (AIP)
	Friedreich's ataxia	AR	uncertain	prominent proprioceptive abnormalities	cardiomyopathy (see hereditary ataxias)

Table 9.27 Hereditary neuropathies secondary to inherited metabolic diseases (contd.)

Pattern of neuropathy	*Underlying disorder*	*Inheritance*	*Metabolic defect*	*Clinical features involved*	*Other systems*
	Ataxia telangiectasia	AR	uncertain	–	scleral telangiectasia, cerebellar atrophy, immunodeficiency, high risk of malignancy
	Giant axonal neuropathy	AR	disorder of intermediate filaments	associated with encephalopathy	-
	Adrenomyelo-neuropathy	X-linked recessive	accumulation of very long chain fatty acids; plasma assay confirms diagnosis	mild neuropathy with spastic paraparesis, may have hearing loss, and leukodystophy on MRI; onset in young adults	hypogonadism, adrenal insufficiency
	Refsum's disease	AR	accumulation of phytanic acid; plasma assay confirms diagnosis	hypertrophic neuropathy with 'onion bulbs' in nerve biopsy	icthyosis, retinitis pigmentosa, deafness
Demyelinating					
	Metachromatic leukodystrophy	AR	defect of Aryl sulfatase A disease	cerebral white matter (leukodystrophy) predominates	–
	Globoid cell leukodystrophy (Krabbe's disease)	AR	defect of beta-galactosidase	cerebral white matter disease (leukodystrophy) predominates	–

Table 9.28 Hereditary motor-sensory neuropathies (HMSN)

Subtype	*Inheritance*	*Site of involvement*	*Clinical features*
HMSN I (peroneal muscular atrophy [PMA]/ Charcot-Marie-Tooth disease [CMT])	AD[1]	axonal and demyelinating	most common HMSN; childhood onset; predominantly motor; atrophy involves leg below mid-thigh, forearms and hand;[2] large fibre type sensory impairment
HMSN II (neuronal form of PMA/CMT)	AD	motor or sensory neuronopathy	less common, later onset; nerve conduction almost normal; otherwise, like type I
HMSN III (Dejerine-Sotta's disease)	AR	predominantly demyelinating; hypertrophic neuropathy with 'onion bulb' formation[3]	rare, onset in infancy ; short stature, hypertrophic (palpable) nerves; may have mental retardation

[1] Two genetic subtypes exist; the common form is due to duplication of the PMP-22 gene on chromosome 17; a rarer variant is due to an abnormality on chromosome 1.

[2] Clinically patient shows pes cavus with hammer toes. Legs have been described as having an 'inverted champagne bottle' appearance or looking 'stork-like'. Claw hand may be seen.

[3] When there are recurrent attacks of segmental demyelination, each attack is followed by Schwann cell proliferation. One Schwann cell undertakes remyelination pushing the others outward; the nerve becomes thickened in areas; on cross-section, the appearance of the myelin sheath resembles an 'onion bulb'.

Infectious Neuropathies

Leprosy is by far the most common cause of infectious neuropathy. A variety of syndromes have been described. A detailed description is provided in the section on infectious diseases.

The lepra bacillus prefers cooler body parts. In tuberculoid leprosy cutaneous receptors are destroyed in the hypopigmented, anesthetic patches. In lepromatous leprosy distal nerves are infiltrated based on their proximity to the skin surface rather than on the axon length. Thus, the dorsum of the hand and the feet may be affected at the same time along with the ear lobes. Pain is lost before touch.

Lyme disease is a newly described tick-borne illness caused by a spirochaete (Borrelia burgdorferi). Infection is acquired when the patient walks in wooded areas. The initial symptoms are a flu-like illness with a characteristic expanding rash (erythema chronicum migrans). In a few weeks to months, 15 per cent of untreated patients develop neurologic abnormalities. The manifestations include meningoencephalitis, chorea, bilateral facial palsy, motor or sensory spinal radiculopathy or mononeuritis multiplex. At this stage, examination of the CSF may show lymphocytic pleocytosis. However, serum antibody titres are usually sufficient to establish the diagnosis. Other late manifestations of Lyme disease include arthritis, and cardiomyopathy. Treatment choices in order of preference are oral doxycycline (100 mg bid) or amoxycillin (500 mg tds) for 14 days. If there is neurologic involvement, the recommended drug is Penicillin G 20 million units/day (in divided doses) for three weeks.

Hereditary Neuropathies

The hereditary neuropathies, a group of slowly progressive disorders, are classified into two groups: in one group, neuropathy is the primary

symptom and no metabolic defect has yet been identified, and in another group the neuropathy is part of an inherited metabolic disease (Table 9.27).

Primary Inherited Neuropathies

These are divided into two main subgroups: the herditary motor-sensory neuropathies (HMSN) and the hereditary sensory neuropathies (HSN).

HMSN is a common disorder and may account for many cases of undiagnosed polyneuropathy. Three types have been described (Table 9.28). HMSN I or II with prominent sensory ataxia (intention tremor) is called the *Roussy-Levy syndrome.*

Refsum's disease has been called HMSN type IV and a hereditary disease combining progressive spastic paraplegia with a peripheral neuropathy has been called HMSN type V.

HSN is also divided into three types (Table 9.29).

Reflex sympathetic dystrophy

Reflex sympathetic dystrophy describes a reflex neurogenic inflammation causing pain, skin changes, bone resorption and joint contractures in the affected limb. There is usually a local or segmental trauma such as a fracture, nerve injury, stroke or myocardial infarction. For an unknown reason, in some patients, this trauma causes sustained sympathetic overactivity. Initially there is burning pain (*causalgia*). Later other changes supervene. The pain responds poorly to analgesics. Treatment is most effective if started early and consists of treating the underlying cause, if possible, with analgesics, antidepressants, aggressive physical therapy and sympathetic blockade. Rarely, surgical sympathectomy may be required. There is usually spontaneous improvement with time.

Mononeuropathy

Mononeuropathy refers to a lesion affecting a single peripheral nerve on one or both sides. It implies a local cause, commonly trauma. The other causes include the category of entrapment neuropathies discussed below, a tumour such as a neurofibroma and Hansen's disease (leprosy). The cutaneous field of various peripheral nerves is shown in Figs 9.28 and 9.29.

Trauma

Trauma may be obvious and acute such as with a stab wound or a compound fracture. In these cases, if there is a neurological deficit due to a nerve lesion, immediate surgical correction is attempted. Trauma may also be repetitive and acute. Pressure on the elbows can damage the ulnar nerve, the use of crutches can cause a lesion of the radial nerve (*crutch palsy*), and high boots can squeeze the peroneal nerve as it curves around the fibular head.

Injury to a nerve may transiently disrupt function (*neuropraxia*), disrupt axonal continuity leaving the endoneurium intact (*axonotemesis*), or disrupt axons and connective tissue sheaths (*neuronotemesis*). The first heals fastest and the last may result in a permanent deficit.

Table 9.29 Hereditary sensory neuropathies (HSN)

Subtype	*Inheritance*	*Site of involvement*	*Clinical features*
HSN I	AD	neuronopathy (dorsal root ganglion)	onset in teens; all sensory modalities impaired; distal ulceration and mutilation; may have sensorineural deafness
HSN II	AR	neuronopathy (dorsal root ganglion)	childhood onset; other features as above
HSN III (Riley-Day syndrome)	AR	dorsal root and sympathetic ganglia	onset at birth; sensory impairment with dysautonomia

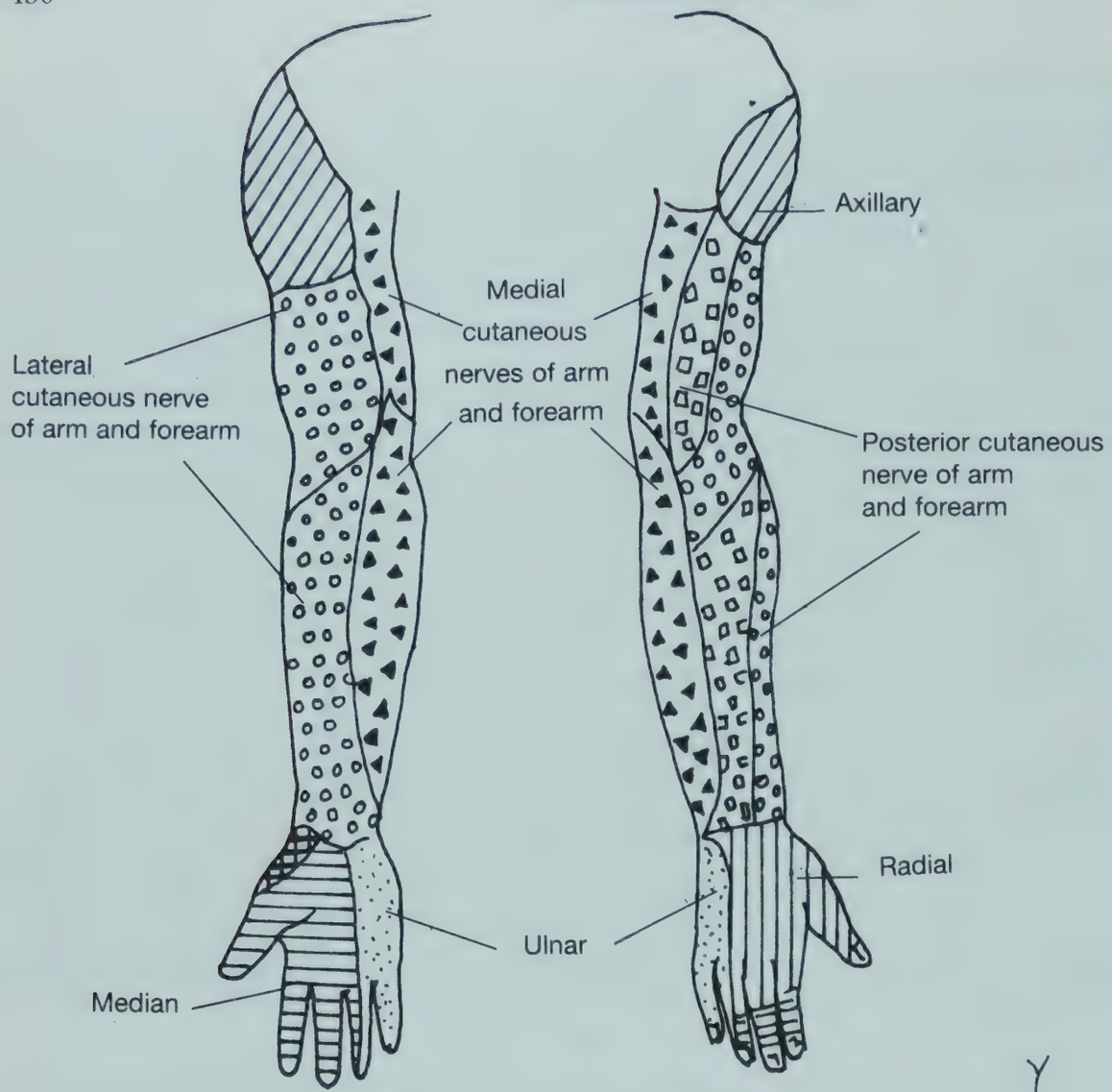


Fig 9.28 Peripheral nerve lesions in the upper limb

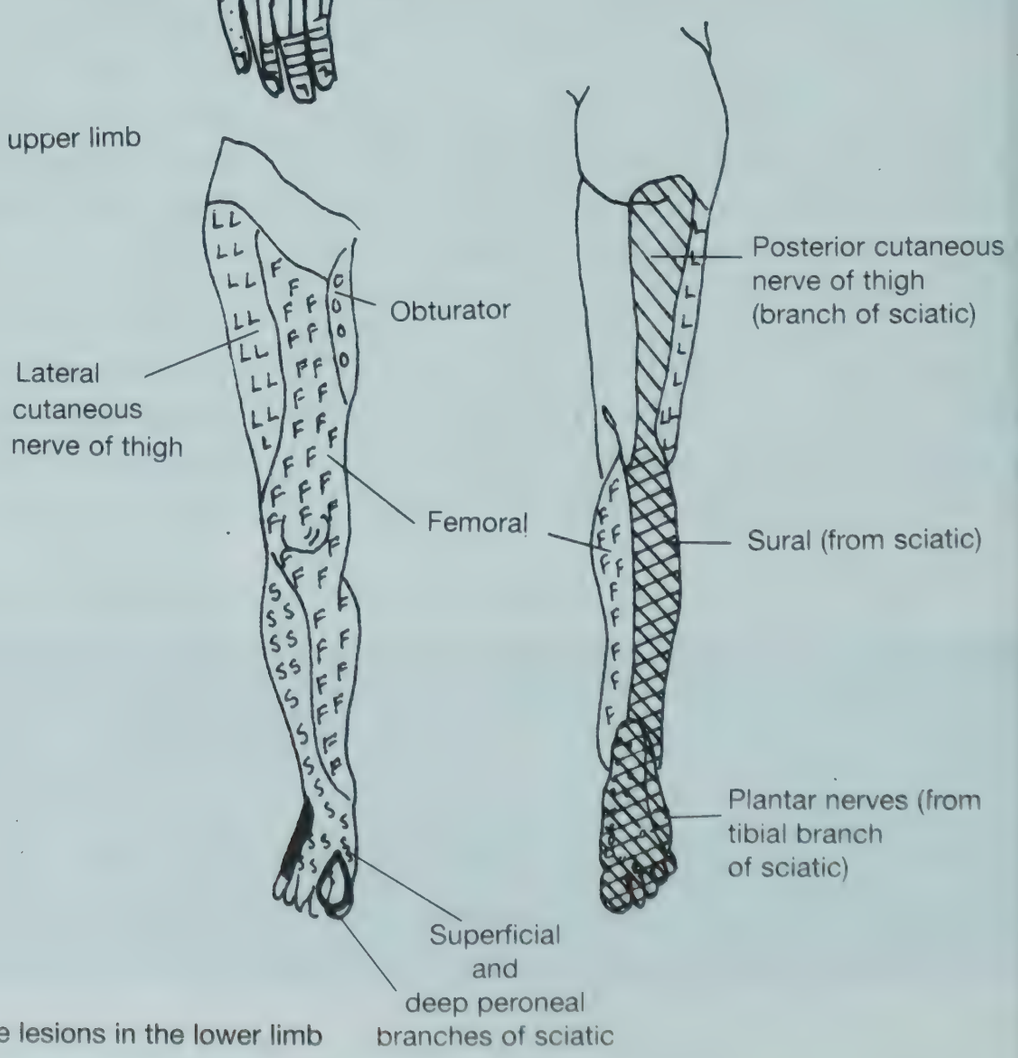


Fig 9.29 Peripheral nerve lesions in the lower limb

Surgery is indicated if the deficit is persistent or worsening and the EMG shows that denervation is continuing.

Entrapment neuropathies

The nerve may be trapped between ligaments, between a ligament and a bone, or between other firm surfaces. Nerves are susceptible at those points where they usually pass through an osseoligamentous canal. Deposition of any substance within this canal increases the chances of a lesion as does repetitive trauma to the nerve within this canal (for example, repeated flexion and extension of the wrist causes trauma to the median nerve as it passes through the carpal tunnel). The causes of entrapment neuropathies are frequent use, repeated minor trauma, hypothyroidism, diabetes mellitus, rheumatoid arthritis, acromegaly, sudden changes in weight, and pregnancy.

The most frequently seen disorder in this category is the **carpal tunnel syndrome**. This is a syndrome of compression of the median nerve at the carpal tunnel. The stress to the nerve may result from everyday activities such as typing, kneading dough and driving. The initial symptoms are tingling and paresthesiae in the fingers which may be sufficiently severe at night to keep the patient awake. The pain may radiate into the arm and forearm. Later, there is sensory impairment over the thenar eminence and the lateral three fingers (particularly the index finger). Still later there is wasting and weakness of the thenar muscles. The first signs of weakness are often in the abductor pollicis brevis. Percussion over the median nerve in the carpal tunnel causes pain (*Tinel's sign*) and hyperextension of the wrist (as in folding hands in a 'namaste' gesture) or hyperflexion can cause pain (*Phalen's signs*).

The diagnosis is made by nerve conduction studies which show a prolonged distal latency in the affected nerve (>4 m/s) as compared to the opposite median nerve or the ulnar nerve at the wrist. Reversible causes such as hypothyroidism are looked for if there is a clinical suspicion of the same. Sometimes an X-ray of the wrist is taken if significant local trauma involving the carpal bones or wrist joint is suspected. The treatment consists of reducing the stress on the nerve (for example, a wrist support may be used while typing), using a wrist splint or crepe bandage to restrict movement at the wrist joint, judicious use of a mild analgesic and, if the neurological deficit progresses, decompressive surgery. The flexor retinaculum is sectioned, a simple procedure which is very effective.

Plexopathies

The nerve roots which will supply the upper limb form the brachial plexus and those which will supply the lower limb form the lumbosacral plexus. From these plexuses arise all the nerves to the limbs. In the plexus, fibres from different roots realign to pass into the nerve they need to join. A lesion involving a root causes a segmental pattern of motor involvement and a dermatomal pattern of sensory loss. A lesion involving a nerve affects the muscles or sensory area innervated by that nerve which may not correspond to any one spinal cord segment. A plexus lesion may involve the distribution of multiple nerves and may affect only parts of these nerves. It may involve several adjacent roots.

Table 9.30 Differentiation between root and plexus lesions

Radiculopathy	*Plexopathy*
Only one root may be affected	More than one root involved
May show signs of cord compression	Usually absent
Typical root pain	Pain along distribution of several roots; no worsening with coughing, sneezing
More likely to be bilateral; often unilateral	Usually unilateral

Brachial plexitis

The brachial plexus is formed by the C5 to T1 nerve roots. The C5 and C6 roots unite to form the *upper trunk*, the C7 root forms the *middle trunk* and the C8 and T1 roots form the *lower trunk*. Each trunk divides into anterior and posterior divisions. The three posterior divisions unite to form the posterior cord, the upper anterior divisions form the lateral cord and the lower anterior divisions form the medial cord. All the nerves to the upper limb arise from these. Lesions affecting the brachial plexus may involve only the upper trunk (*Erb's palsy*), only the lower trunk (*Klumpke's palsy*) or both (*Parsonage-Turner syndrome*).

Erb's palsy is typically congenital and usually follows a hyperabduction injury to the shoulder during a difficult birth. The child grows up with an upper limb that hangs in a position of internal rotation and extension at the elbow (*waiter's tip position*). *Klumpke's palsy* may be congenital or acquired, due to a tumour at the apex of the lung. In the latter case it is associated with a Horner syndrome.

Acute inflammatory brachial plexitis or *brachial amyotrophy* begins with shoulder and neck pain. In a few days muscle weakness rapidly develops, typically affecting the deltoid, biceps, triceps and the serratus anterior. Grip strength may be diminshed which helps to distinguish the lesion from the two common differential diagnoses considered: a C5, C6 disc prolapse and a *rotator cuff shoulder joint arthritis*. Tendon reflexes are diminished. Sensory involvement may or may not be seen. An EMG and nerve conduction studies establish the diagnosis. There is no effective therapy. Gradual recovery occurs over 3–24 months. A traumatic injury to the plexus merits surgical correction. In some patients vaccines, radiotherapy and malignancy can cause brachial plexitis.

Thoracic outlet syndrome consists of pain and weakness in a C8, T1 distribution due to stretching of the lower cord usually over an anomalous cervical rib. An X-ray and nerve conduction can help establish the diagnosis. Surgical resection can be done. Most patients with cervical ribs are asymptomatic.

Lumbosacral plexitis involves the lumbosacral plexus (formed from T12 to S3 roots). The most common cause is a pelvic pathology such as cancer, hematoma, aneurysm or pelvic surgery. It can occur after a normal vaginal delivery (*parturitional*). Diabetes and vasculitis can also cause this syndrome. Clinical evaluation should include a pelvic and rectal examination and assessment of inguinal lymph nodes.

Mononeuropathies: some individual nerve lesions

Ulnar nerve lesions cause wasting of the hypothenar eminence and interossei of the hand and sensory impairment over the medial and fourth and fifth fingers of the hand. Forearm sensory loss suggests a root lesion. Conversely, if only the lateral surface of the fourth finger is anesthetic the lesion is in the ulnar nerve and not the nerve root. The medial edge of this finger is also supplied by the C8 root but through the median nerve. This is an example of how the difference between dermatomal and root patterns can help us localise a lesion. In an ulnar nerve lesion the patient may have a claw hand. The fourth and fifth fingers are maximally clawed (hyperextension at metacarpophalangeal joint and flexion at interphalangeal joints). Causes include pressure at the cubital tunnel, leprosy and vasculitis.

Radial nerve lesions cause weakness of the triceps, supinator, thumb abductors and extensors of the wrist and fingers. The result is a wrist drop. There is a sensory loss in the so-called 'anatomical snuff box' — the area between the extensor tendons to the thumb and index fingers. The causes include pressure on the nerve (a drunken person sleeping with an arm hanging over the edge of the bed would sometimes awaken with such a lesion, also called '*Saturday night palsy*'), and lead poisoning.

Meralgia paresthetica is a syndrome of painful paresthesiae over the anterolateral thigh due to entrapment of the lateral cutaneous nerve of the thigh as it passes through the inguinal ligament. There may be mild objective sensory loss. There is no motor deficit. The causes include obesity, diabetes mellitus and pregnancy. Treatment strategies include reassurance, advising weight loss and, in rare cases, local steroid injections.

Femoral neuropathy weakens the iliopsoas and quadriceps femori and causes sensory impairment over the area shown in Fig 9.28. The causes include diabetes mellitus and a psoas mass or hematoma.

A sciatic nerve lesion may result from injury or an injection abscess. The hamstrings (knee flexors) and all the leg muscles are weak. The area of sensory loss is shown in Fig 9.29 and includes the posterior thigh, the posterolateral part of the leg and the sole of the foot.

A lesion of the common peroneal causes a foot drop and sensory impairment over the lateral leg and dorsum of foot. The causes include trauma, leprosy and vasculitis.

The causes of acute generalised paralysis could be:

1. Lesion of cervical spinal cord or craniovertebral junction
2. Poliomyelitis
3. Guillain-Barre syndrome
4. Myasthenia gravis: myasthenic or cholinergic crisis
5. Botulism
6. Snakebite (Elapidae)
7. Hypokalemic paralysis
8. Rhabdomyolysis

The causes of symmetric predominantly distal muscle weakness* could be:

1. Amyotrophic lateral sclerosis
2. Peroneal muscular atrophy (HMSN or Charcot-Marie-Tooth disease)
3. Myotonic dystrophy
4. Inclusion body myositis
5. Scapuloperoneal dystrophy

* The presence of sensory involvement or asymmetric involvement should prompt a search for other causes involving the spinal cord or peripheral nerve.

KEY CONCEPTS

Muscle

➢ Muscular weakness may be of an upper or lower motor neuron type. The *upper motor neuron* type of deficit suggests spinal cord or supraspinal lesions, is characterised by spasticity (the flexors are stronger in the upper extremity while the extensors are dominant in the lower extremity), hyperreflexia and extensor plantar responses. The *lower motor neuron* type of deficit may arise due to disease of the anterior motor neurons, a radiculopathy, plexopathy, peripheral neuropathy, myopathy or disease of the neuromuscular junction; these deficits are associated with varying combinations of segmental weakness, hypotonia, atrophy, fasciculations, flexor plantar responses and reduced deep tendon reflexes.

➢ In neurogenic weakness due to *anterior horn cell disease,* fasciculations are prominent, atrophy is marked while sensations are intact. A *radiculopathy* is characterised by radicular pain and a dermatomal pattern of deficit. *Peripheral neuropathies* are characterised by distal weakness, prominent sensory deficits (usually) and absent deep tendon reflexes. In *myopathic disorders,* the weakness is symmetric, proximal muscles are involved more, sensations are normal and fasciculations are absent; deep tendon reflexes are diminished to an extent commensurate with the muscle weakness.

Muscle biopsy

➢ The biopsy of a clinically 'mild to moderately' involved muscle aids the diagnosis of myopathies, polymyositis, sarcoidosis and polyarteritis nodosa.

Nerve biopsy

➢ Sural nerve biopsy is helpful in establishing a diagnosis of neuritic leprosy, vasculitis (clinical evidence of

mononeuritis multiplex) and some hereditary neuropathies (amyloidosis).

Nerve conduction velocity

- In this technique, a peripheral nerve is stimulated at several points along its course and the time to initiation of muscle contraction is measured; *distal latency* is the time required to traverse the nerve segment nearest to the muscle.
- In *demyelinating* neuropathies, there is a significiant slowing of nerve conduction with focal demyelinating blocks. Axonal neuropathies are identified by relative preservation of conduction velocity, spontaneous activity on the EMG and a low amplitude evoked response.
- The repetitive stimulation of a nerve assesses fatiguability of the neuromuscular junction; a decremental response is observed in myasthenia gravis while an incremental response is obtained in the Eaton-Lambert syndrome.

Electromyogram

- The EMG is a recording of the electrical activity of the muscles (which is displayed on an oscilloscope) during the insertion of a needle electrode, with the muscle at rest and during muscle contraction.
- The resting muscle is electrically silent. With minimal muscle contraction, single motor unit action potentials appear; with increasing contraction, these potentials form an interference pattern.
- In muscle disease, the interference pattern is full but the amplitude is reduced. In nerve disease, there is increased insertional activity and spontaneous activity (fibrillations/fasciculations), a reduced interference pattern (fewer motor units recruited), and giant action potentials.

Amyotrophic lateral sclerosis

- This is a disease characterised by degeneration of the upper and lower motor neurons resulting in a *pure motor deficit.*
- The signs of a lower motor neuron type of deficit are wasting of muscles and fasciculations. Upper motor neuron signs are spasticity and increased deep tendon reflexes. There is no involvement of the bladder, voluntary eye movement or sphincters.
- The onset is usually in the sixth decade or later. Weakness of the distal musculature is greater than that of the proximal muscles; upper limb involvement exceeds that of the lower limb. Bulbar symptoms may occur due to involvement of the brainstem nuclei.
- The diagnosis is clinical. EMG findings include fibrillation, fasciculation and giant motor units.
- Treatment is symptomatic. Riluzole is a new therapeutic agent but its benefit is marginal.

Spinal muscular atrophy

- SMA is an inherited group of disorders (gene on chromosome 1) characterised by skeletal muscle wasting secondary to degeneration of the anterior horn cells and brainstem motor nuclei.
- Three variants are described. *Werdnig-Hoffman disease* is an autosomal recessive disease with onset in infancy (2–4 months); hypotonia and delayed milestones are important features. *Intermediate SMA* has a later onset (by age 2 years) than above but none of the children can walk or crawl. *Kugelberg-Welander disease* has an onset between the age of 2–17 years; weakness and wasting of lower extremities is characteristic, the arms being affected to a lesser extent.
- The diagnosis is clinical and can be confirmed by an EMG (denervation pattern without peripheral nerve involvement).
- There is no specific treatment; supportive measures may be instituted.

Duchenne muscular dystrophy

- This is an X-linked recessive disease characterised by weakness of the pelvic and shoulder girdle muscles; the basic defect is the absence of the gene product *dystrophin* in the sarcolemma.
- Males manifest the disease at the age of 3–7 years; features include a waddling gait, frequent falls, difficulty in climbing stairs. *Pseudohypertrophy* of the calves is typical.
- The progression of the disease is rapid and the patient is wheelchair-bound by the age of 10–12 years. Additional features include mild mental retardation and a cardiomyopathy.
- CPK levels are markedly elevated even in the preclinical stage.
- Management is supportive. Prenatal counselling (fetal sex determination and dystrophin immunoblotting) is important.

Becker's dystrophy

- This is a clinical variant of Duchenne dystrophy; onset is at the age of 5–15 years and the disease has a milder course. Patients have dystrophin of abnormal molecular weight.

Facioscapulohumeral dystrophy

- This autosomal dominant disease (gene on chromosome 4) manifests with weakness of the facial and shoulder girdle muscles.
- The onset is at the age of 10–20 years with difficulty in eye closure, whistling and arm elevation.

Myotonic dystrophy

- This autosomal dominant disease (gene on chromosome 19; increased CTG trinucleotide repeats) is characterised by *myotonia* (abnormal slow

relaxation after voluntary muscle contraction) and muscle weakness.

- ➢ The facial appearance is typical; there is bilateral ptosis, wasting of the temporalis and frontal balding. Myotonia is prominent in the hand muscles and manifests as an inability to relax the hand after a handshake.
- ➢ There is an increased prevalence of cataracts, testicular atrophy, mental retardation, cardiac conduction abnormalities and diabetes mellitus.
- ➢ The diagnosis is clinical. The EMG shows the typical *dive bomber* sound.
- ➢ Phenytoin/quinidine/procainamide may help myotonia. Active and passive exercises are recommended.

Polymyositis-dermatomyositis

- ➢ Polymyositis is an inflammatory disease of the skeletal muscles characterised by symmetric proximal weakness. Clinically, *dermatomyositis = polymyositis + rash* (lilac-coloured and extending over the upper eyelids). Serologic evidence of *anti-Jo-1* antibodies may be present.
- ➢ Its histologic features are myocyte necrosis, varying fibre sizes, perifascicular degeneration and perivascular infiltration with lymphocytes (the latter two in DM). *Inclusion body myositis* is characterised by hypertrophied myofibres with vacuoles containing peripheral granules (on EM).
- ➢ There is clinical evidence of proximal muscular weakness affecting the shoulder girdle, the hip, and sometimes the neck. Pharyngeal and laryngeal muscle involvement may result in dysphagia and dysphonia. Respiratory muscle involvement is of ominous significance. *Gottron's patches* are red scaly patches over the extensor surfaces. Distal weakness and diminished tendon reflexes may be seen in inclusion body myositis
- ➢ The diagnosis is clinical. CPK levels are elevated and the EMG shows spontaneous fibrillation, increased insertional activity and positive sharp potentials. Biopsy features are as described above.
- ➢ Treatment is with high dose corticosteroids. CPK levels are the best guide to efficacy of therapy. Azathioprine may be used in refractory cases.

Myasthenia gravis

- ➢ Myasthenia is a disease characterised by episodic muscle weakness caused by autoimmune damage to the acetylcholine receptors in the postsynaptic neuromuscular junction.
- ➢ An association of myasthenia with thyrotoxicosis, autoimmune disorders and with thymoma has been described.
- ➢ Typically, the ocular, bulbar and proximal limb muscles are involved. The muscular weakness is episodic, showing fatiguability and diurnal variation. There may be exertion induced ptosis, diplopia, dysarthria, dysphonia and nasal regurgitation. The patient may complain of a difficulty in elevating her arms above the shoulders or in climbing stairs. Occasionally, only the ocular muscles may be involved (*pure ocular myasthenia*). Sensations are intact, sphincter function is normal and deep tendon reflexes are preserved.
- ➢ A *Tensilon test* helps confirm the diagnosis. An EMG reveals a decremental response with repetitive nerve stimulation. A single fibre EMG shows increased jitter. Serum antiacetylcholine receptor antibodies are detected in the majority of patients.
- ➢ Anticholinesterase drugs are used for relief of symptoms but do not alter the course of the disease. Plasmapheresis may be used in refractory cases for symptomatic relief. Thymectomy, corticosteroids and immunosuppressants favourably modify the course of the disease.

Eaton-Lambert syndrome

- ➢ This syndrome is associated with visceral malignancies (small cell lung cancer most often). The primary defect is a reduced release of acetylcholine from the presynaptic portion of the neuromuscular junction.
- ➢ Limb muscles are typically involved while the ocular and bulbar muscles are spared. Deep tendon reflexes may be diminished.
- ➢ An *incremental pattern* on repetitive nerve stimulation is highly suggestive.
- ➢ Treatment with guanidine hydrochloride may be attempted.

Familial periodic paralysis

- ➢ This covers a spectrum of autosomal dominant disorders characterised by episodic flaccid arreflexic paralysis without an alteration in consciousness or sensations. There is an association with hyperthyroidism in Asian males.
- ➢ Three forms are described based on the values of serum potassium obtained during the episodes.
  - ➢ *Hypokalemic* type: the attacks are precipitated by vigorous exercise or a carbohydrate meal. The weakness lasts 24–48 hours.
  - ➢ *Hyperkalemic* type: attacks are less severe, shorter but more frequent and are provoked by fasting. Myotonia may be present.
  - ➢ *Normokalemic* type: resembles the hyperkalemic variant.
- ➢ The diagnosis is by history and by documenting abnormal values of serum potassium during the episode. Attacks can be provoked in an ICU setting with a glucose-insulin infusion (for the hypokalemic type) or with potassium chloride (for the hyperkalemic type) with ECG monitoring and availability of ventilatory assistance.

- ➢ Acetazolamide can prevent episodes in both hypo- and hyperkalemic types of disease. Oral potassium may be administered during attacks in the hypokalemic type of disease.

Peripheral neuropathy

- ➢ This is a syndrome of sensory loss, muscle weakness and vasomotor abnormalities (alone or in combination) arising from a disease of the peripheral nerves.
- ➢ The disorder may involve a single nerve (mononeuropathy; e.g. pressure palsies, entrapment neuropathies), multiple nerves in separate areas (*mononeuritis multiplex* resulting in asymmetric deficits; causes include diabetes, leprosy, vasculitis, immunoinflammatory disease, Sjogren syndrome, sarcoidosis, HIV infection and Lyme disease), or multiple nerves simultaneously (*polyneuropathy;* causes include diabetes, leprosy, alcoholism, uremia, amyloidosis, nutritional deficiencies, immunoinflammatory disease, metabolic diseases [Refsum's disease, Tangier's disease] and familial neuropathies).
- ➢ Polyneuropathies often present with relatively symmetric deficits; involvement of the distal muscles is greater than that of the proximal muscles and the lower extremities are more often involved than the upper extremities.
- ➢ Management includes treatment of the underlying specific cause (antimicrobials for leprosy, steroids for immunoinflammatory disease and vasculitis), splinting (for pressure palsies) and surgical decompression (for entrapment neuropathies).

Guillain-Barre syndrome (LGB/AIDP)

- ➢ This is an acute ascending, rapidly progressive demyelinating polyradiculoneuropathy, possibly of autoimmune origin. There may be a history of preceding viral infection, surgery or vaccination.
- ➢ There is histologic evidence of focal, segmental demyelination with perivascular and endoneurial lymphocytic infiltration.
- ➢ Clinically, there is evidence of relatively symmetrical paresis beginning in the legs and progressing to the arms. Sensations are normal and the sphincters are spared. Respiratory muscle involvement is of ominous significance.
- ➢ The diagnosis is clinical. The differential diagnosis includes porphyria, botulism, diphtheria, tick bite and polio.
- ➢ The CSF typically shows increased protein without an increase in cell count (*albuminocytologic dissociation*). The EMG shows slow nerve conduction and prolonged F wave latencies.
- ➢ Supportive care is vital. ICU admission is important if there is respiratory muscle involvement. Plasmapheresis and intravenous immunoglobulins are beneficial if adminstered early in the course of the disease.

Hereditary sensorimotor neuropathy Type 1 (Charcot-Marie-Tooth disease)

- ➢ An autosomal dominant disease of peripheral nerves characterised by weakness and atrophy predominantly affecting peroneal and distal leg muscles.
- ➢ The onset is in childhood with foot drop, progressive *stork-like* deformity, areflexia and *glove and stocking* sensory deficit. The peripheral nerves are enlarged and palpable.
- ➢ Segmental demyelination-remyelination results in slow nerve conduction.

Hereditary sensorimotor neuropathy Type III (Dejerine-Sotta's disease)

- ➢ This is an autosomal disorder manifesting in childhood. It resembles HMSN Type I but is rarer, and motor weakness progresses at a faster rate. Peripheral nerves are palpable and have an *onion bulb* appearance on biopsy.
- ➢ The treatment is mainly supportive. Orthopedic measures to stabilise the feet and occupational rehabilitation are important measures.

9.10 Disorders of the cranial nerves

A review of brainstem anatomy is suggest as a prelude to understanding this section (Fig 9.30a).

The Olfactory Nerve

The first cranial nerve is the olfactory nerve. It is tested by assessing if the patient can identify the presence of an odour and then asking her to identify the type of odour. Small vials filled with familiar substances such as coffee may be used. 'Scratch and sniff' booklets are also available. An irritative substance such as ammonia should not be used as it can stimulate trigeminal afferents in the mucosa. A lesion of the olfactory nerve (*anosmia*) manifests as a decreased appreciation of foods (food does not 'taste' as well because normal taste partly depends on appreciating the aroma of the food). Anosmia may occur following head injury, and in Alzheimer's disease.

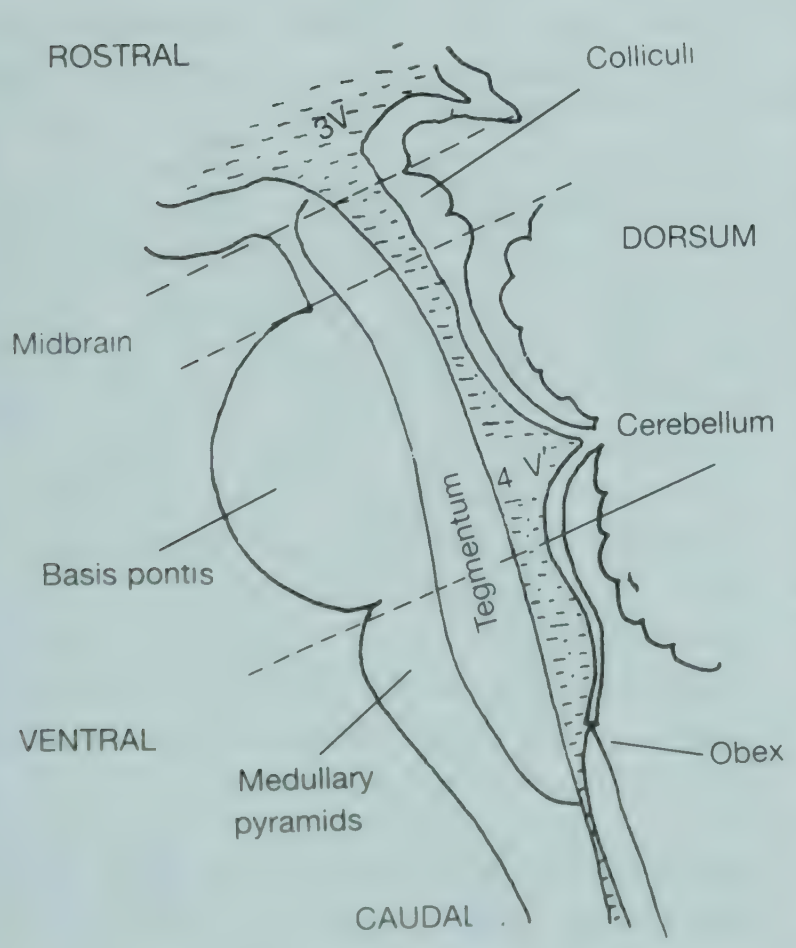


Fig 9.30a Sagittal section through the brainstem

The Optic Nerve

The optic nerve carries visual impulses from the retina. A complex visual pathway consisting of the optic tract and the optic radiations helps the optic nerve transmit these impulses to the occipital cortex. Embryologically, the optic nerve is part of the central rather than the peripheral nervous system and, hence, is affected by processes specific to the central nervous system such as multiple sclerosis. A clinical examination of the optic nerve includes assessment of *visual acuity, visual fields*, and *fundus examination*. These three aspects will be discussed here. More detailed testing may rarely be required and would include examination of *colour vision* and *contrast sensitivity*. Visual acuity is the capacity to accurately distinguish the form of an object on which a patient is fixating. The image of the object falls on the fovea. Visual acuity may be tested using a Snellen chart, a variety of test 'types' (cards with letters of different sizes on them, each size corresponding to a particular visual acuity) or by

the ability to distinguish the lines on a grating pattern. In patients with some degree of impairment, visual acuity may be tested as the capacity to count fingers, detect movement, or distinguish light from dark. The *visual field* is the area within which the patient can detect an object while he is fixating straight ahead. Defining a defect in the visual field can be very helpful in localising a lesion along the visual pathway. It should be recalled that since there is a convex lens within the eye, any object in one part of the visual field forms an image on the opposite part of the retina. The image of the temporal visual field falls on the nasal part of the retina and the superior part of the field forms an image on the inferior part of the retina.

Normal anatomy of visual pathways (Fig 9.30b) In the retina all axons converge on the optic disc. The largest number come from the macula forming a biconvex *maculopapillary bundle*. Fibres from the temporal retina curve above and below this bundle to reach the disc. The fibres do not cross a horizontal midline. The optic nerve begins behind the optic disc and enters the skull through the optic foramen alongwith the ophthalmic artery and vein. A branch of the ophthalmic artery called the central retinal artery penetrates into the optic nerve, divides into branches after emerging at the optic disc and then supplies most of the retina. At the optic foramen the optic nerve is surrounded by the structures in the superior orbital fissure. The two optic nerves run medially and meet at the *optic chiasma*, which lies just anterior to the hypothalamus and above the pituitary gland. Posteriorly, the optic chiasma divides into the right and left *optic tracts*. The axons in the optic nerve partially decussate at the optic chiasma. Fibres from the temporal half of the macula and retina continue into the ipsilateral optic tract. These fibres are carrying images from the nasal half of the visual field. Fibres from the nasal half of the retina (temporal half of the visual field) cross in the optic chiasma to enter the contralateral optic tract. Thus, if an object is to the right of a patient's midline its image will fall on the nasal half of the right retina and the temporal half of left retina as shown in the figure. The impulses from both eyes enter the left optic tract, those from the left eye passing directly and those from the right eye crossing at the chiasma. During this chiasmal crossing, fibres from the inferior portion of the retina (superotemporal part of visual field) extend anteriorly for a short distance into the opposite optic nerve as *von Willebrand's knee*. The optic tract passes posterolaterally to the *lateral geniculate body* where most of the fibres terminate. The optic radiations arise from the lateral geniculate and pass posteriorly to the visual cortex on the medial surface of the occipital lobe (*calcarine cortex*). The fibres from the inferonasal part of the retina loop forward into the temporal lobe around the inferior horn of the lateral ventricle (*Meyer's loop*) before passing posteriorly to the calcarine cortex. The fibres from the superonasal part of the retina lie in the parietal lobe for part of their course.

The visual field defects associated with a lesion at different sites can be predicted based on the anatomy of the visual pathways (Fig 9.30b). Complete loss of vision in one eye (called *amblyopia*) implies a lesion anterior to the optic chiasma. Lesions behind this can cause blindness only if they are bilateral, otherwise they will cause field defects. If the maculopapillary bundle is affected there is a *central* scotoma (involving macular vision) or a *cecocentral* scotoma involving the area between the centre of fixation (macula) and the blind spot (optic disc). Such lesions are seen in drug or toxin induced visual loss (for example, ethambutol induced or nutritional amblyopia). Lesions of the temporal retina form an *arcuate* scotoma because of the arching course of the fibres (seen in glaucoma and optic atrophy secondary to papilledema). If such defects extend they still respect the midline causing *altitudinal* scotomata (for example, with an embolus to one branch of the central retinal

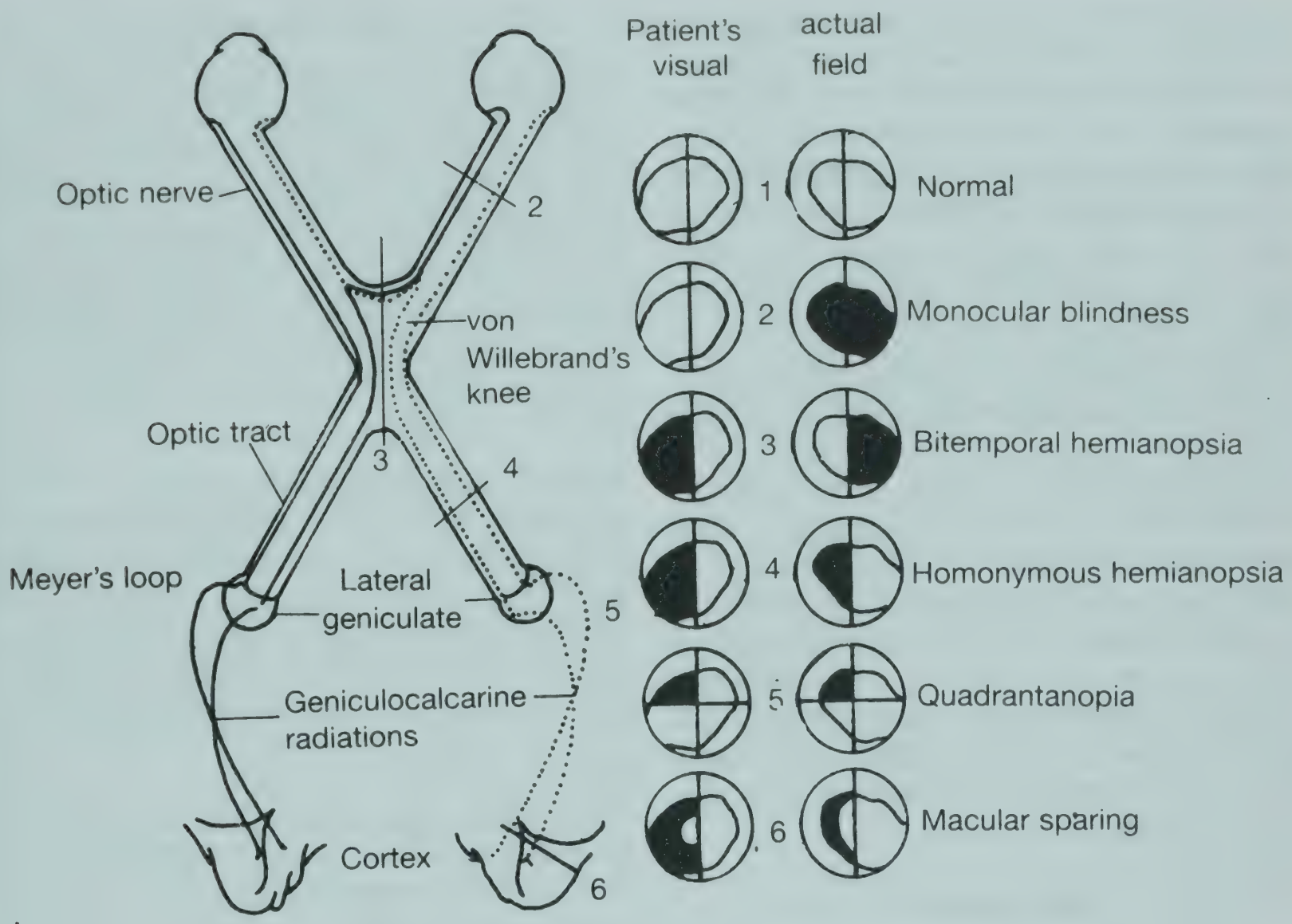


Fig 9.30b The visual pathway and common lesions causing visual field deficits

artery). A lesion of the optic nerve causes a visual impairment over the entire visual field in that eye. A lesion posterior to the chiasma causes a discrete vertical midline scotoma in the visual field. A lesion affecting the chiasma and starting in the midline, causes a *bitemporal hemianopia* (crossing fibres are involved). Causes include a pituitary tumour, craniopharyngioma or an aneurysm of the anterior communicating artery. A lesion affecting the junction of the optic nerve with the chiasma (*junctional scotoma*) causes an ipsilateral complete visual loss with a contralateral superotemporal visual field defect (due to involvement of von Willebrand's knee). A lesion behind the chiasma causes *homonymous hemianopia.* Vision is lost in the contralateral half of the visual field. If the visual field, as charted, is symmetrical in each eye, the field defect is said to be *congruous* and this suggests a lesion close to the occipital cortex. More anteriorly, fibres from corresponding points on the retina in each eye may run at some distance from each other. A lesion involving Meyer's loop involves part or all of the upper lateral quadrant in the visual field. Because it looks like a slice cut out of a circular pie and because it is located superiorly, it is called a '*pie in the sky*' defect. A lesion in the parietal lobe causes a '*pie on the floor*' defect. The causes of lesions in the optic radiations and in the cortex are strokes and tumours. A cortical hemianopia may be associated with some macular sparing due to bilateral representation of macular fibres. Any of these classical patterns may be seen in an incomplete form. Visual fields are examined

using a common object such as a finger or a round object of 0.5 cm diameter on a slender stick or pin. The patient is asked to fixate on the examiner's eye or nose and tell if he can simultaneously detect the object of interest in his peripheral visual field. This method of testing is called the *confrontational* method. The visual field is tested with both eyes open (binocular field) as well as with one eye covered. In an uncooperative patient, the hand is waved in each quadrant, close to the patient's face. If vision is grossly intact in that quadrant, there is a reflex blink (*menace reflex*). Finer testing may be achieved using a machine that moves a visual stimulus over the field (*kinetic perimetry*) or a number of points of light, each in turn gradually growing in intensity until the patient detects it (*static perimetry*). There are different perimeters, a popular one being the Goldman perimeter. The central 30 degrees of the visual field may be explored in greater detail using a Bjerrum screen.

Optic Atrophy

A non-inflammatory lesion of the optic nerve fibres causes a visual loss associated with a pallor (colour change from yellowish to white) of the optic disc and sharply defined disc margins on fundoscopy. A cause of abrupt onset bilateral optic atrophy is methanol poisoning (discussed in Chapter 18). A subacute onset occurs with optic atrophy which may be caused by chloramphenicol, ethambutol or heavy metals. Very insidious onset in a young patient suggests a hereditary cause such as *Leber's optic atrophy* (a mitochondrial disease). Pressure or ischemia of an optic nerve may cause unilateral or bilateral optic atrophy (following chronic meningitis, a granuloma in the superior orbital fissure or an optic nerve glioma/ meningioma). A tumour of one sphenoid ridge may cause optic atrophy in the ipsilateral eye and papilledema due to raised intracranial pressure in the opposite eye.

Optic Neuritis

An inflammatory lesion of the optic nerve causes visual loss, and is associated with redness and swelling of the fundus if the lesion is close to the optic disc (optic neuritis), and no discernible abnormality of the fundus if the lesion is placed further posteriorly (*retrobulbar neuritis*). Optic neuritis may be idiopathic. It may be associated with a transverse myelitis (*neuromyelitis optica* or *Devic syndrome*), or it may develop into multiple sclerosis.

Anterior ischemic optic neuropathy

This entity refers to visual loss due to infarction of the optic nerve. It is of sudden onset, painless and is seen in elderly patients. The disc appears swollen with peripapillary hemorrhages. Causes include diabetes, atherosclerosis and temporal arteritis. There is an altitudinal field defect.

Papilledema

Papilledema is the swelling of the optic disc due to raised intracranial pressure. There is a loss of normal venous pulsations, the 'cup' at the centre of the disc gets filled, the margins of the disc become blurry often beginning at the nasal edge, and later there may be flame-shaped hemorrhages and superficial infarcts (cotton wool spots). If the disc is very swollen, the power of the lens may have to be adjusted on the ophthalmoscope to focus on the surface. Papilledema is distinguished from optic neuritis by the relative preservation of visual acuity until late. Congenital abnormalities of the disc can result in an appearance resembling papilledema (pseudo-papilledema).

The causes of visual impairment also include glaucoma, cataracts, retinitis pigmentosa, retinal detachment, macular degeneration and obstruction of the central retinal artery and vein.

The Oculomotor (third), Trochlear (fourth) and Abducens (sixth) Cranial Nerves

The oculomotor nerve arises from a midline nucleus in the rostral midbrain at the level of the

superior colliculus. It supplies motor fibres to most of the extraocular muscles of the eye. There are also parasympathetic fibres arising from a nucleus adjacent to the oculomotor nucleus called the *Edinger-Westphal nucleus* which innervate the muscles responsible for pupillary constriction and accommodation of the lens.[1] The third nerve emerges medially in the interpeduncular fossa, runs over the crus cerebri on the ipsilateral side, past the posterior cerebral and posterior communicating arteries to pierce the dura and enter the cavernous sinus. Thence it passes through the superior orbital fissure into the eye. The pupillary fibres run in the dorsomedian part of the nerve. Compressive lesions affect the muscles of eye movement as well as the pupil. The artery to the nerve runs through the centre of the nerve substance. An ischemic lesion due to diabetes mellitus spares the pupils. An involvement of only *some* of the muscles supplied by the third nerve suggests a lesion within the brainstem or within the orbit. In the other parts, nerve fibres supplying the different muscles are too close together to be selectively spared.

The fourth cranial nerve arises from a nucleus in the dorsal part of the caudal midbrain (level of inferior colliculus). The axons run dorsally and decussate in the anterior medullary velum (where they are susceptible to trauma during head injury). This is the only cranial nerve exiting dorsally from the brainstem. It crosses the superior cerebellar artery and then runs close to the third nerve to enter the orbit.

The sixth cranial nerve is a pure motor nerve and arises from a pontine nucleus to reach an eye muscle responsible for ipsilateral gaze. It leaves the brainstem at the pontomedullary junction, pierces the dura at the petrous apex and runs through the cavernous sinus and superior orbital fissure into the orbit. A lesion at the petrous apex involves both fifth and sixth cranial nerves. The sixth nerve is particularly susceptible to injury in patients with raised intracranial tension because it runs a taut course between the two tethering points at the pontomedullary junction and the petrous apex.

Examination of eye movements

In human beings the eyes can move in either direction, up and down and each eye can also rotate. These movements are made possible by six extraocular muscles which tether the eyeball to the orbit. The various muscles, their action and innervation can be understood by reviewing Fig 9.31 and Table 9.31.

Intortion refers to inward movement of the upper midpoint (12 o'clock point) on the eyeball towards the nose. *Extortion* refers to outward movement of this point. The superior muscles are intorters of the eyeball while the inferior muscles extort the eyeball. The action of the recti and the oblique muscles depend on the position of the eyeball. When the eye is abducted, the recti mediate the 'up and down' movements. When the eye is adducted, the oblique muscles mediate elevation and depression of the eyeball. The two oblique muscles are connected to the posterior part of the eyeball. This explains why the superior oblique pulls the posterior part of the eyeball upwards, tilting the anterior part downwards. Elevation and depression of the eye should be assessed not only in the primary position (looking straight ahead) but also at the extremes of adduction and abduction. The assessment should include movement of each eye individually (called *ductions*) and movement of both eyes together (called *versions*).

The control of eye movements and the coordination of the two eyes depends on the perfectly synchronous functioning of a complex system. In humans there are a variety of eye movements all of which subserve a single function, to project the image of the object of interest on to the fovea. We explore our visual environment with a series of rapid conjugate eye

[1] Accommodation is due to a muscular body called the ciliary body which arises from the iris and normally keeps the lens capsule stretched. Contraction of this muscle allows the lens to become more convex permitting near vision.

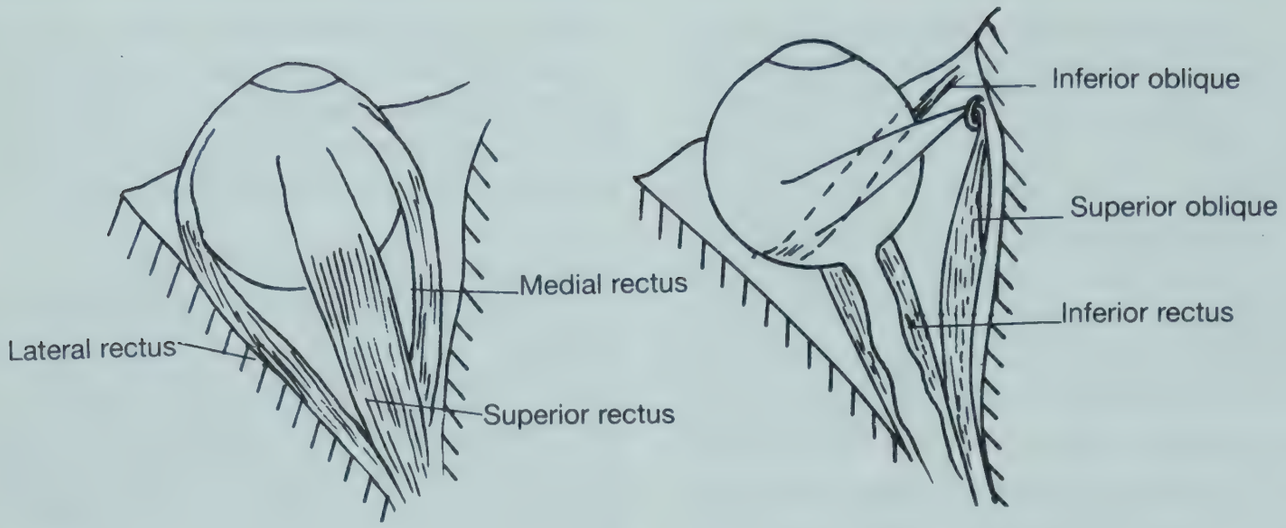


Fig 9.31 Muscles attached to the left eye

movements which project different objects in turn on to our fovea. These movements are called *saccades* and are initiated in the *contralateral* frontal lobe (area 8). If we wish to keep on looking at an object as it moves in our visual field, we need to track the object with a smooth pursuit movement of our eyes in the same direction. This involuntary movement is mediated by the anterior portion of the ipsilateral occipital cortex. In addition if we wish to go on looking at an object while our head or bodies move (for example, when we are in a train looking out) we need to integrate stimuli from our optic nerves (*optokinetic reflex*) and our vestibular system (*vestibular reflex*) with our oculomotor control. The third and fourth nerve nuclei are in the midbrain, the sixth nerve nucleus is in the pons and the vestibular nuclei are in the medulla. They communicate rapidly with one another on the same side and across the midline through fibres in the *median longitudinal fasciculus (MLF).*

The two eyes need to move together. Usually their visual axes remain parallel. Such movements are called *conjugate eye movements.* Impulses from the frontal or occipital cortex reach the brainstem gaze centres by way of the corticobulbar fibres. The gaze centres then direct the corresponding muscles on the two sides to contract in unison resulting in conjugate gaze in the desired direction. Pairs of muscles which act together are called *yoke* muscles. Thus, the lateral rectus of the right eye and the medial rectus of the left eye contract together

Table 9.31 Action (on the eyeball) and innervation of extraocular muscles

Muscle	*Innervation*	*Primary action*	*Secondary action*
Lateral rectus	abducens	abduction	-
Medial rectus	oculomotor	adduction	-
Inferior rectus	oculomotor	depression	extortion
Superior rectus	oculomotor	elevation	intortion
Inferior oblique	oculomotor	extortion	elevation
Superior oblique	trochlear	intortion	depression

resulting in movement of both eyes to the right. Hence they are 'yoked' together. The gaze centres for lateral gaze are located in the ipsilateral pons adjacent to the sixth nerve nucleus (*parapontine reticular formation*). The gaze centre for upward and downward gaze are close to the third nerve nuclei in the midbrain. The left pontine gaze centre sends impulses to the right third nerve nucleus through the left MLF, the fibres crossing over in the midbrain close to the third nerve nucleus. The impulse sent to the yoke muscles in the ipsilateral and contralateral eyes are equal in intensity (*Hering's law*). The intensity of these impulses is determined by the fixating eye. If, however, one of the yoke muscles is weak (due to a nerve lesion), the neural impulse moves it to a smaller degree than on the normal side and the eye movement becomes dysconjugate. The image of an object does not fall on the usually corresponding points of the retina. This results in a sensation of seeing two versions of an object one knows to be single (*diplopia*). One of these images is usually less well-defined than the other and can be identified as the *false image.* If the diplopia is present even with one eye covered (*uniocular* diplopia), one should determine the nature of separation of the images (horizontal or vertical), the degree of separation and the position in which the separation is maximal. If the separation of the images is uniform in all positions of gaze, it is called *concomitant strabismus*. Concomitant strabismus is of childhood onset. If the separation is more in one direction *non-concomitant strabismus* is suspected and suggests an acquired neurological lesion. One of the muscles activated in this position of maximal separation of images is the paretic muscle. Thus if the images are maximally separated on looking to the left, the paretic muscle must be the left lateral rectus or the right medial rectus. The image from the paretic eye is always projected further from the midaxis. If a red glass is placed in front of one eye (by convention the right) and a white light used as a stimulus, the image due to the right and left eye can be separated as the image from the right eye will look red. If in the above example the image to the left is red (and the one closer to the midline is white), it is the right medial rectus which is weak. The assessment of a strabismus using diplopia depends on the patient's cooperation. There are other objective techniques available. Patients with diplopia may adopt a compensatory head posture. The head is turned so that the weak muscle has to contract less. Thus, with a left lateral rectus palsy the head will be turned to the left. With weakness of the recti the neck is flexed (superior rectus) or extended (inferior rectus). A lesion of one superior oblique makes the patient tilt her head towards the opposite shoulder. A light is shone on both pupils and the position of the corneal reflection in relation to the pupils assessed (*Hirschberg's test*). An asymmetry suggests strabismus. One eye is covered and the other allowed to fixate on an object such as a pen. Then the second eye is uncovered and allowed to fixate while the first eye is covered. Normally, neither eye moves with the uncovering. In strabismus the covered eye moves to fixate since the axes of the two eyes are not parallel. One problem in the assessment of diplopia is sorting out the lesion when multiple nerves are involved. Isolated lesions of the fourth and sixth nerves are easy to identify. A frozen eyeball suggests involvement of all the nerves on one side. Involvement of more than one muscle makes third nerve involvement likely, particularly if adduction or elevation of the eye is impaired. Determining if there is concomitant fourth nerve lesion in this situation can be difficult. A neuroophthalmologist may chart ocular movements in detail, by using the a *Hess screen* and chart torsional abnormalities using the *Maddox rod test.* In myasthenia gravis the ocular palsies are bilateral, may vary from day to day and be associated with ptosis, weakness of eye closure, facial muscles and swallowing. Pure ocular myasthenia can occur. Injection of edro-

phonium (*Tensilon test*) transiently corrects the ptosis, strabismus and diplopia.

Disorders of dynamic eye movements Voluntary saccadic initiation should be tested by having the patient look from side to side. The speed of initiation (latency), accuracy and velocity of the saccades are assessed. The patient is asked to fixate on one object while another distracting stimulus is moved quickly across the visual field and the ability to suppress reflexive saccades is noted. *Smooth pursuit* is tested by asking the patient to follow a small target at a distance of one metre while keeping the head still. The target should be moved at a slow uniform speed. A lesion of the pursuit system results in insufficient initial pursuit which is corrected by a 'catch up' saccade. Hence the pursuit movement is jerky (saccadic) rather than smooth. Abnormalities of dynamic eye movements occur with lesion of the cerebellar and extrapyramidal systems or frontal and occipital cortex. They are discussed under these sections. They can be recorded using *electrooculography* or EOG. This technique relies on the fact that the eyeball acts as an electric dipole. Electrodes are placed on either side of the eye and the voltage between them changes as the eyes move giving a record of the velocity and amplitude of movement.

Opsoclonus is an acute-onset disabling disorder characterised by numerous, involuntary saccadic movements in all directions. These movements persist during sleep. There is often associated truncal ataxia resulting in a 'opsoclonus-myoclonus' or '*dancing eyes and dancing feet' syndrome*. The cause may be an acute encephalitis (often without altered sensorium) or a paraneoplastic syndrome (from a neuroblastoma, small-cell lung cancer or breast carcinoma).

Nystagmus

Nystagmus is a repetitive to and fro movement of the eyes. It is due to a failure of the normal integration between the pursuit eye movement system and the vestibular system. Usually the nystagmus consists of a slow movement away from the primary position followed by a quick corrective movement that brings the eye back to its original position. Usually it is the slow drift that is pathological. However, by convention nystagmus is classified according to the direction of the quick component. Nystagmus may be up and down (vertical) or side to side (horizontal). Nystagmus that occurs when the patient is looking straight ahead is called *primary position nystagmus* whereas nystagmus that is only evoked by sustained lateral gaze is called *gaze-evoked* nystagmus. In evaluating nystagmus it must be remembered that a few jerks at more than 30 degrees away from the midline may be physiological. The direction of the quick phase should be noted; also note the gaze position in which the nystagmus is maximal and whether it is symmetrical or of higher amplitude in one eye. Nystagmus present since birth (*congenital nystagmus*) is typically horizontal, of equal amplitude in both directions (*pendular*) and damped by convergence. Acquired nystagmus has a quick and a slow component (*jerk nystagmus*). It is often due to a lesion in the posterior fossa. In gaze-evoked nystagmus, the quick component is towards the direction of gaze. This is seen with antiepileptic medication (when the nystagmus is of equal amplitude in both directions) and in ipsilateral cerebellar disease[1] (where the amplitude of nystagmus is greater on looking towards the lesion). Primary position vertical nystagmus has some localising value. *Downbeat* nystagmus suggests a lesion of the cervicomedullary region while *upbeat* nystagmus suggests a lesion of the rostral medulla and pons. A primary position *horizontal nystagmus* suggests a vestibular lesion and a primary position *torsional* or *rotatory nystagmus* (intorsion-extorsion nystagmus) is seen with a lateral medullary lesion. In peripheral vestibular disease the nystagmus is typically precipitated by

[1] Causes include a lateral medullary syndrome on that side, a cerebellopontine angle tumour and cerebellar infarction.

head movements, has a torsional component (mixed nystagmus) and is curbed by fixation.

The Pupil

The pupil is an aperture in the iris which regulates the amount of light entering the eye. It dilates in dim light and constricts in bright light. In addition the pupil constricts with near vision because, the smaller the aperture, the sharper will be the image. There are two muscular diaphragms in the iris, the pupillary constrictor muscles activated by the parasympathetic efferents and the pupillary dilator muscles activated by the sympathetic efferents. The parasympathetic efferents arise in the midbrain (Edinger-Westphal nucleus) and run with the third nerve as described earlier. There is a midbrain pupilloconstrictor centre which receives afferent input from the optic nerve and sends impulses to the Edinger-Westphal nucleus. Bright light stimulates pupillary constriction (light reflex). The sympathetic fibres arise in the hypothalamus and pass caudally along the lateral tegmental region of the brainstem on the same side, into the cervical spinal cord, exit along with the ventral thoracic spinal roots (T1,T2), synapse in the stellate ganglion and then run along the carotid artery to the cavernous sinus where they join the nasociliary branch of the fifth nerve and enter the eye. The pupils are normally symmetrical since both pupils respond simultaneously to light. The response of the ipsilateral pupil is called the *direct* response and the response of the contralateral pupil is called the *consensual* response.

Pupillary asymmetry is called *anisocoria.* If it is due to a sympathetic nervous system lesion, one pupil is abnormally small (miotic) and the anisocoria increases in dim light which should normally cause dilatation. Such a lesion is also associated with ptosis (drooping of the upper eyelid) of the eye since one of the lid elevators called Muller's muscle is innervated by the sympathetics. This combination is called a *Horner syndrome* and may be caused by a lesion anywhere along the sympathetic efferent pathway. The ptosis is only partial unless the third nerve (which supplies the other lid elevator, the levator palpebrae superioris) is also affected. If pupillary asymmetry is due to a parasympathetic lesion it is more marked in bright light when the abnormal pupil fails to constrict. Abnormal pupillary dilation is called *mydriasis.* In addition to nerve lesions and lesions within the CNS (some of which are discussed in the section on 'pupillary abnormalities in the differential diagnosis of coma') pupillary abnormalities may be due to systemic (bilateral) or local (unilateral) administration of pharmacologic agents. Thus, if a patient has recently had an ophthalmological evaluation her pupils may have been dilated by the doctor to permit a fundus examination. Agents used include muscarinic anticholinergic agents (atropine, homatropine) and adrenergic agonists (tropicamide). Similarly, a common cause of a small pupil is the use of medication for glaucoma. Pilocarpine (a cholinergic agent) or timolol (a beta adrenergic blocker) may be used. A patient who has undergone cataract surgery or one who has had uveitis may have an irregularly shaped pupil (*corectopia*). In the latter case there will be adhesion between the iris and cornea or lens (synechiae).

The fibres in the optic nerve mediating the light reflex leave at the midbrain level. Hence, a lesion of the occipital cortex, which causes blindness (no conscious perception of light) would leave the pupillary response intact. This is a reliable way of distinguishing cortical blindness. A partial lesion of one optic nerve causes a *Marcus Gunn* pupil or 'afferent pupillary defect'. A flashlight is rapidly swung from eye to eye. The affected eye sends fewer optic nerve impulses in response to the light than the normal eye. Hence, in the affected eye, pupillary constriction due to the consensual response is more powerful than pupillary constriction due to a direct response and the abnormal eye may actually show paradoxical dilatation as the flashlight swings in front of it.

A lesion in the dorsal midbrain (tectal region) can interrupt the pathway between the centre mediating the light reflex and the Edinger-Westphal nucleus (the pretecto-oculomotor tract). The pupillary constriction in response to convergence is due to simultaneous activation of the medial rectus and pupillary constrictors in the oculomotor nucleus and is independent of the pretecto-oculomotor tract. Hence, in this situation the light reflex is lost but accommodation is retained. This is seen in syphilis (*Argyll-Robertson* pupil), in diabetes mellitus and with structural lesions of the tectal region.

DISEASES OF THE CRANIAL NERVES

The Trigeminal Nerve

The trigeminal is a complex nerve which serves both sensory and motor functions.

Sensory function

The trigeminal nerve carries superficial and deep sensory impulses from the entire face (except for the small portion shown in Fig 9.32), the anterior half of the scalp (anterior to the coronal suture) and the mucous membranes of the eye (cornea and conjunctiva), nose and mouth. There are three peripheral sensory branches, their areas of distribution being shown in Fig 9.32. All three branches extend proximally to enter the middle cranial fossa, but each branch enters through a different foramina in the skull. The V_1 or *ophthalmic* division enters through the superior orbital fissure, the V_2 or *maxillary* division enters through the foramen rotundum and the V_3 or *mandibular* branch enters through the foramen ovale. Peripheral afflictions such as herpes zoster and trauma to the skull can, therefore, affect a single peripheral branch without affecting the other. The three branches lie close together within the cavernous sinus. Hence diseases affecting this anatomical area—the parasellar region—frequently affect all three branches, sometimes in a sequential fashion. Finally, all three branches join as the cell bodies of fibres in all three peripheral branches lie with a single sensory (dorsal root) ganglion – the *Gasserian ganglion*, also called the semilunar ganglion. This ganglion lies in a dural fold called *Meckel's cave*. The artery lies in close proximity to the ganglion and sometimes a tortuosity of the artery results in a loop of the artery lying directly over the ganglion. Some neurosurgeons believe that pressure from arterial pulsations in this overlying vessel results in the syndrome of trigeminal neuralgia.

The proximal branches from these sensory neurons arising within the ganglion enter the brainstem and divide into two tracts. The touch, pressure and vibration fibres ascend a short distance to synapse in the pontine *principal sensory nucleus* of the trigeminal. Tactile and pain fibres descend as the spinal tract of the trigeminal nerve. They synapse in the *nucleus of the spinal tract*– an elongated nucleus running adjacent to the nerve. Fibres from the peripheral portions of the face descend the farthest, extending down to the cervical spinal cord (C2 level). Pain and temperature fibres from the area around the nose descend only a short distance into the medulla. Fibres from the *nucleus of the spinal tract* — second-order neurons — cross over to the opposite side at the level in which they arise and then ascend upwards as the most medial portion of the spinal lemniscus. Fibres from the principal sensory nucleus also cross over to ascend in the most lateral portion of the medial lemniscus. Together, all the ascending axons carrying sensory input from the trigeminal area constitute the *trigeminothalamic tract*. Lesions affecting crossing fibres, such as syringomyelia, can therefore involve only those trigeminal fibres crossing at a particular spinal level while sparing those crossing higher. Thus, in syringomyelia, with a cervical cord cavitation, pain and temperature may be lost only in the peripheral areas of the face (*onion skin pattern* of sensory loss, Fig 9.33).

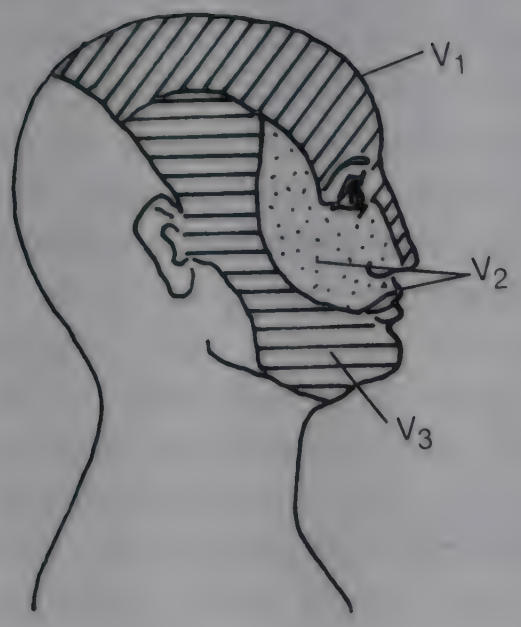


Fig 9.32 Areas supplied by the three peripheral sensory branches of the trigeminal nerve

Fig 9.33 'Onion skin' pattern of sensory impairment over face

Proprioceptive afferents from the trigeminal area ascend with the pressure and vibration fibres but synapse in a separate nucleus– the *mesencephalic nucleus* of the trigeminal, located as its name indicates, in the midbrain.

Motor function

The motor portion of the sensory nerve has its origin in the trigeminal motor nucleus located in the midpons. The fibres pass beneath the Gasserian ganglion and become part of the mandibular nerve. They innervate the masseter and pterygoids (ipsilateral lateral pterygoid and medial pterygoid). A lesion of one trigeminal nerve results in deviation of the jaw to the same side when an attempt is made to open the jaw against pressure.

Reflexes

Reflexes mediated by the trigeminal nerve include the corneal and conjunctival reflexes (superficial) and the jaw jerk which is a deep tendon reflex, mediated entirely by the fifth nerve. The afferent portion of the corneal reflex is mediated by the trigeminal while the efferent portion is mediated by the seventh (facial) nerve. This information can be used to deduce which nerves are affected, as shown in Table 9.32.

Trigeminal neuralgia

Trigeminal neuralgia, also called *tic douloureux*, is characterised by recurrent, brief spasms of intense pain felt along the distribution of the maxillary and sometimes also the mandibular branches of the trigeminal nerve.

Table 9.32

Nerve(s) affected	*Right corneal*		*Left corneal*	
	Direct	*Consensual*	*Direct*	*Consensual*
Right trigeminal	Absent	Present	Present	Absent
Right facial	Absent	Absent	Present	Present
Right trigeminal and facial	Absent	Absent	Present	Absent

Epidemiology The disorder typically manifests in late middle age but may occur earlier.

Clinical features The paroxysms of pain are intense and may be precipitated by sensory stimuli (even gentle stimuli such as a puff of wind) or motor movements of a portion of the face. Between paroxysms there may be a residual dull ache. Sleep may be disturbed and the patient may become depressed and may consider suicide. On examination there is typically no sensory or motor paralysis.

Etiopathogenesis Most cases are idiopathic. In 10 per cent of the idiopathic cases a blood vessel is seen to lie over the nerve root but the significance of this fact is uncertain. Lesions within the brainstem (such as multiple sclerosis) and lesions at the cerebellopontine angle (such as tumours) need to be excluded. Danger signals suggesting an underlying etiology include young age at onset, the presence of objective neurological findings (sensory loss, absent corneal reflex) and the concomitant occurrence of hemifacial spasm with pain–*tic paroxisif*.

Treatment Carbamazepine and phenytoin are often effective in reducing the frequency and severity of the paroxysms. Second-line drugs include sodium valproate, clonazepam and baclofen. There are several surgical ablative techniques available. The choice and the frequency of the method depends on the philosophy and experience of the treating centre. All surgical techniques result in anesthesia over the affected region.

The techniques include:

1. alcohol or phenol injection of the affected nerve close to the foramen ovale and rotundum;
2. a stereotactic approach to thermocoagulation of the affected root;
3. surgical resection of the affected root;
4. decompression of root by a posterior fossa approach (moving overlying vessel).

The Facial Nerve

The seventh cranial nerve or the facial nerve i both sensory and motor. Motor fibres travel t the muscles of facial expression and parasym pathetic efferents regulate the secretion of th salivary and lacrimal glands. It carries sensor signals from the salivary and lacrimal glands taste from the anterior two-thirds of the tongue and cutaneous sensation from a small area behind the external ear. Cutaneous sensory fibres have their cell body in the geniculate ganglion. The course of the facial nerve is show in Fig 9.34a which also explains why lesions a different sites may involve only the motor fibre to the face (lesion at A), these along with th taste fibres to the tongue (lesion at B),[1] and both these along with impaired secretion of tear an salivary glands (lesion at C). A lesion of th seventh nerve below the nucleus cause weakness of the entire ipsilateral half of the fac (lower motor neuron lesion). A lesion of th corticobulbar fibres causes weakness of onl the muscles in the lower half of the face an spares eye closure because the muscles to th periorbital area receive corticobulba innervation from both motor cortices (uppe motor lesion of seventh nerve) (Fig 9.34b).

Bell's palsy

The most common cause of unilateral faci paralysis of the lower motor neuron type is syndrome called Bell's palsy. The disease affec 1% of all individuals at some time in their life.

Clinical features The onset of symptoms sudden. Typically the patient has been expose to cold weather or is aware of some retr auricular pain. A day or two later, she awake with a unilateral facial palsy. The angle of th mouth droops, the nasolabial fold is flattene the cheek appears fuller on the affected side, th eye is opened wider and the creases on th

[1] A lesion here can also cause '*hyperacusis*'—abnorm sensitivity to sounds due to a lesion of the nerve to t stapedius.

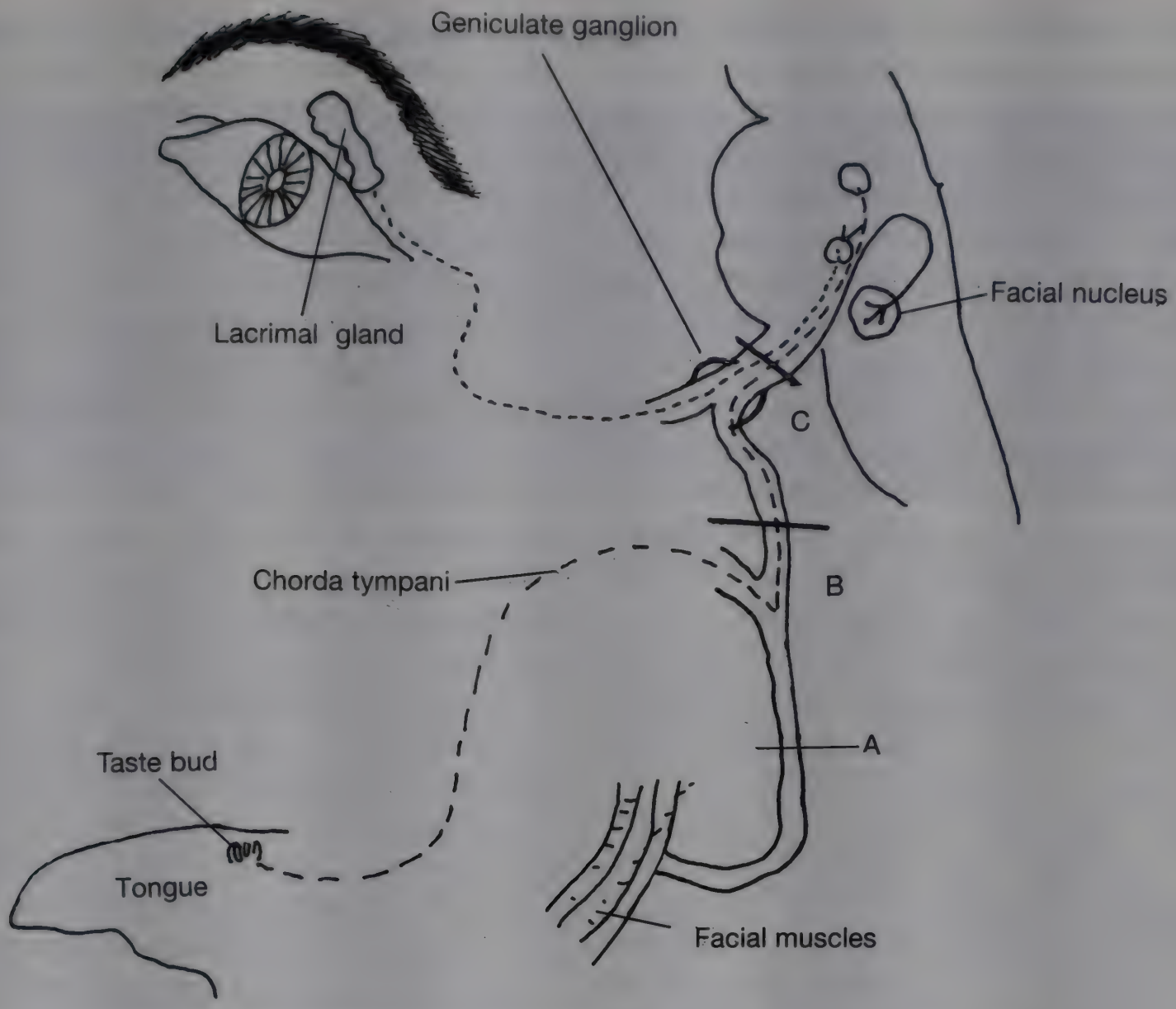


Fig 9.34a Course of the facial nerve and effect of lesions at different sites

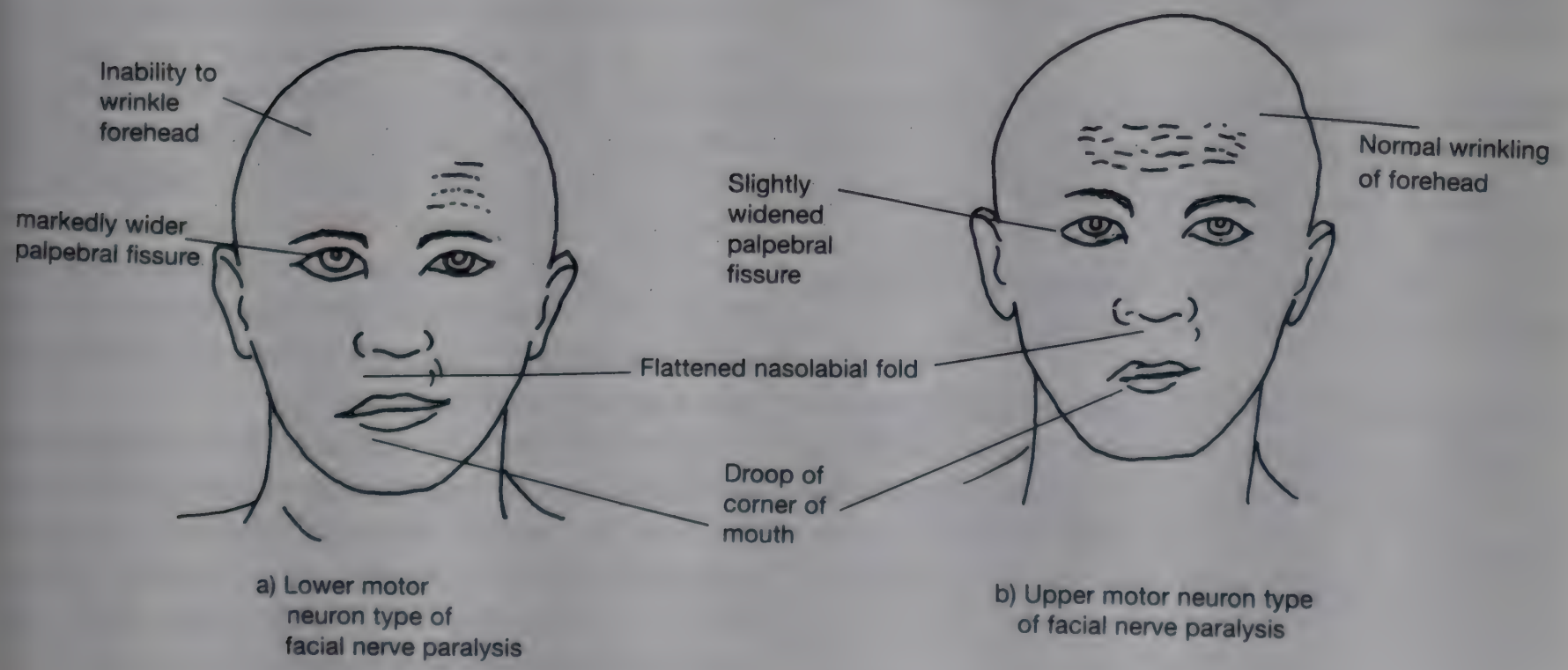


Fig 9.34b Facial nerve paralysis

forehead are erased over the affected half. When the patient tries to speak or smile the defect becomes more obvious as one half of the face will not move. If the patient attempts to close her eye, the eyeballs roll up (*Bell's phenomenon*). There may be increased tearing from the affected eye and drooling of saliva from the corner of the mouth. In milder cases, eye closure may be possible but the lashes are not buried despite asking the patient to 'keep her eyes closed as tightly as possible' and the affected eye can be more easily opened by the examiner than the unaffected eye. The ability to puff cheeks and to whistle are impaired. The patient may complain that the face feels numb but no objective sensory impairment is found on testing. Taste may be impaired on the affected side. Usually, patients make a spontaneous recovery over a few weeks. The milder the initial paresis, the greater the chances of complete recovery. In 10 per cent of patients the facial paresis persists indefinitely. With the passage of time there may be a contracture on the affected side. Aberrant nerve regeneration may lead to tearing in association with chewing or salivation (called 'crocodile tears' or *Bogorad's phenomenon*). Similarly there may be eye closure every time the jaw is opened (*jaw-winking synkinesis*).

Pathophysiology The cause is not known but it is now thought that the disease may represent a form of reactivation of a latent herpes virus infection. An MRI picture shows swelling of the facial nerve within the stylomastoid foramen. The CSF may show a few lymphocytes.

Investigations No investigations are necessary to prove the diagnosis in most cases. An EMG performed after 10 days may help determine the prognosis. If there is evidence of denervation, incomplete (rather than full) recovery becomes more likely.

Treatment If the patient presents in the first week and has more than a minimal deficit, prednisone at a dose of 60 mg daily is administered for 5 days and tapered over the next 5 days. This may hasten recovery. The eye should be protected from injury. This may include using artificial tear drops, using glasses to protect the eye from dust and an eye-patch when the patient sleeps. Massage or electrical stimulation of the weakened muscles may hasten recovery. A tape is sometimes used as a facial splint to improve the patient's appearence.

Differential diagnosis Other causes of facial nerve palsy of the lower motor neuron type include leprosy, the *Ramsay-Hunt* syndrome (herpes zoster vesicles over the auditory meatus and facial palsy), and lesions of the temporal bone and cerebellopontine angle (as will be discussed under the eighth cranial nerve). Recurrent palsies affecting both sides may be idiopathic or due to sarcoidosis. Bilateral facial weakness may be seen with the Guillain-Barré syndrome. Myasthenia and myotonic dystrophy may simulate bilateral facial weakness but there is also ptosis which is not seen with a seventh nerve lesion.

The Eighth Cranial Nerve

The eighth cranial nerve is the vestibulocochlear nerve. It is a sensory nerve carrying afferent impulses from the cochlea in its auditory component and afferent impulses from the utricle, saccule and semicircular canals in its vestibular component. Both components run closely together through the temporal bone and enter the brainstem at the level of the pontomedullary junction where the vestibular and auditory pathways diverge.

Dizziness may be defined as an unpleasant sensation due to uncertainty of one's position or motion in space. Normal position sense is dependant on the integration of input from the inner ear and the eyes with input from the various cutaneous and proprioceptive afferents. An abnormal input from any one of these sources can result in a feeling of dizziness. The

The differences between central and peripheral vertigo are :

Peripheral vertigo	*Central vertigo*
Prominent associated symptoms of nausea, vomiting, sweating	Mild
Improved by visual fixation	No
There is a torsional component to the associated nystagmus	May be absent
Hearing impairment, tinnitus are more common	Long tract signs may be present

sensation may be classified into four categories: true vertigo, faintness or near syncope, ataxia or imbalance and finally non-specific light headedness. Only true vertigo will be discussed in this section. The causes of syncope are discussed under the cardiology section and the various disorders of the peripheral nerves, spinal cord, cerebellum and basal ganglia which can cause unsteadiness are discussed in those sections. In elderly individuals, dizziness might occur due to a combination of factors: mild peripheral neuropathy, decreased vision due to cataracts, impaired proprioceptive input from the cervical spine due to spondylosis, nutritional anemia, multiple medications and cardiac arrhythmia. All reversible causes should be treated.

Vertigo is a sensation as if one has just got off a merry-go-round; either the patient herself or surrounding objects appear to spin. The patient feels ill and nauseous, may vomit and finds it hard to stand. Vertigo is caused by a structural or functional disturbance of the vestibular pathway. Examination frequently shows nystagmus and *past-pointing.*[1]

Motion sickness is a physiological form of vertigo that occurs when unfamiliar movements of the head and body overwhelm the vestibular system. Variants include bus or car sickness, sea sickness and airplane sickness. It may be prevented by oral ingestion of an antihistamine such as diphenhydramine, half an hour before the expected stimulus. A scopolamine patch is available in some countries and is effective for 12 hours. Scopolamine and antihistamine drugs both work due to their anticholinergic effects.

Pathological vertigo may be due to a problem with the labyrinths, the eighth nerve or the vestibular nuclei and ascending vestibular pathways within the brainstem. Vertigo due to a lesion outside the brainstem is called *peripheral vertigo*; vertigo due to a lesion within the brainstem is called *central vertigo.* Lesions which are supratentorial rarely cause vertigo. One exception is the aura of vertigo which may be seen in complex partial seizures arising from the temporal lobe.

Labyrinthine dysfunction: *Acute unilateral labyrinthitis* may be due to an inner ear infection, trauma to the base of the skull, a vertebrobasilar stroke (usually associated with hearing impairment; sometimes with a lateral medullary syndrome), or it may be idiopathic following a viral flu-like illness. Recurrent unilateral labyrinthitis may result in episodes of isolated vertigo (*vestibular neuronitis*) or vertigo with hearing loss and a low-pitched tinnitus (*Meniere's disease*). Both these syndromes typically occur in middle aged or elderly adults. There is episodic accumulation of endolymph, the cause for which is not clear. Each attack resolves in a few days but the patient is left with some hearing impairment

[1] The patient is asked to point to the examiner's outstretched finger with his own.

until finally he becomes deaf in that ear. Bilateral labyrinthitis may be due to drugs such as streptomycin, gentamicin and quinine which damage the hair cells in the cochlea and semicircular canals. In all types of peripheral vertigo, head movements can worsen the symptoms. However, in one type of vertigo called *benign paroxysmal positional vertigo* (BPPV), the vertigo only occurs when the patient assumes a specific posture. Sitting up or lying down may bring on the symptoms but the symptoms resolve in about one minute. During the same period that the patient experiences the vertigo, examination reveals torsional nystagmus. The vertigo may be induced by the *Nylen-Barany maneuver.*[1] The symptoms usually subside in a few weeks to months. The cause of BPPV is postulated to be an otolith that becomes loose and floats around in the semicircular canal stimulating hair cells whenever a certain posture is assumed.

Eighth nerve lesion

Compression of the vestibulocochlear nerve at the cerebellopontine angle is seen with tumours of this region. The most common tumours are a neurofibroma and a meningioma. On careful examination there may be associated hearing impairment, absent ipsilateral corneal reflex (5th nerve lesion), cerebellar signs, a lower motor neuron type of seventh nerve paresis or papilledema.

Brainstem vertigo: Central causes of vertigo include vertebrobasilar TIAs (associated with at least one other brainstem symptom) and multiple sclerosis.

Clinical evaluation should include testing of hearing and otoscopy to ensure that the ear drum is intact. Once this is ascertained, caloric testing or an ENG (*electronystagmogram*–details in books on otorhinolaryngology) can confirm that the lesion is in the labyrinth and identify if it is unilateral or bilateral. If a tumour in the cerebellopontine angle is suspected, a contrast enhanced CT scan or MRI is taken. Caloric testing is done with the patient supine. The external auditory meatus is checked to ensure that the tympanic membrane is intact. The head is flexed to 30 degrees to bring the 'horizontal' semicircular canal to the horizontal plane. 100–200 ml of warm water (44°C) or cold water (30°C) is infused into the patient's ear. The normal response in an awake patient is a slow tonic deviation of the eyes towards the side of the cold water irrigation (or away from the warm water) followed by a phasic quick movement away from the cold water (or towards the warm water). Such phasic responses are not seen in comatose patients. If one canal does not respond adequately to warm or cold stimulation it suggests a *canal paresis*. If the nystagmus is less marked on looking to one side there is a lesion of the vestibular nerve or system on the opposite side; this is called *directional preponderance.*

Management includes rest (in acute vertigo) and an antihistamine such as meclizine (12.5–25 mg tid). A mild sedative (diazepam 2–5 mg) may be useful. In Meniere's disease, a low-salt diet may be tried.

Hearing

Hearing depends on air conduction of the sound waves upto the middle ear and bone conduction thereafter upto the cochlea where action potentials are generated. The primary sensory ganglia are in the *spiral ganglion* of the cochlea and their afferent axons pass in the cochlear portion of the eighth nerve to the dorsal and ventral cochlear nuclei in the medulla. Thence second-order neurons decussate (the decussation is called the *trapezoid body*) and ascend in the contralateral side as the *lateral lemniscus* to the inferior colliculus and thence to the medial geniculate body. Third-order neurons arise here and pass as the *auditory radiation* to the auditory cortex. Since only some fibres cros

[1] The patient sits on the examining table and the doctor then quickly moves him to a supine position with his head hanging over the edge of the table and face turned 45 degrees. There is vertigo and nystagmus after about 10 to 40 seconds and both resolve in a few minutes. The procedure should be repeated with the face turned to the opposite side.

in the trapezoid body there is bilateral representation above this level and deafness only results from lesions of the middle or inner ear, the cochlear nerve or nuclei. Hearing loss due to a lesion in the ear drum or middle ear results in *conductive hearing loss.* This is easily corrected using a hearing aid. Common causes are chronic otitis media and otosclerosis (an abnormal ossification of the area around the stapedial foot plate). Hearing loss due to damage to the cochlea is called cochlear hearing loss and hearing impairment due to a nerve lesion is called retrocochlear hearing loss. Both cochlear and retrocochlear types of hearing loss are called *sensorineural hearing loss* and are not helped by hearing aids. The causes of sensorineural hearing loss include congenital deafness, congenital rubella, a variety of inherited degenerative diseases, chronic exposure to loud noise, fractures of the temporal bone, ototoxic drugs (gentamicin, furosemide, quinine), chronic meningitis, cerebellopontine angle tumour, infarct of the cochlear nerve and Meniere's disease. Tests for hearing include the patient's ability to hear a whisper from six feet with the opposite ear closed, and tests using a 512 Hz tuning fork. Normally, a patient hears the tuning fork placed close to his external auditory meatus better than if it is placed on the mastoid (air conduction better than bone conduction). In conductive hearing loss, bone conduction is better than air conduction on the affected side. This is called a positive *Rinne's test*; thus a negative Rinne's test is normal. In normal subjects, a tuning fork placed over the middle of the forehead (*Weber's* test) is heard equally well in both ears. If one ear has a conductive hearing impairment, the fork is heard better in the affected ear since distracting sounds do not reach that ear. If one ear has sensorineural deafness the fork is heard better in the, unaffected ear. Thus, the 'lateralisation' of the sound on Weber's test can help distinguish between conductive and sensorineural hearing impairment. A more detailed assessment can be achieved by using different types of audiometry and tympanometry.

Tinnitus is the perception of sound in the absence of an external stimulus. The causes include exposure to loud noises (for example, industry), Meniere's disease (low pitched tinnitus), aspirin (high pitched tinnitus), acoustic neurofibroma or without any identifiable cause (idiopathic). Pulsatile tinnitus may occur with a vascular tumour in the posterior fossa. There is no effective treatment. A bland sound or background music may be supplied using a 'tinnitus masker'.

The Glossopharyngeal Nerve

This is the ninth cranial nerve. It carries sensory afferents from the pharyngeal region, taste fibres from the posterior third of the tongue and is also a motor nerve. It carries motor fibres to the stylopharyngeus and the parotid salivary gland.

Glossopharyngeal neuralgia resembles trigeminal neuralgia but is much rarer. The pain is precipitated by swallowing and is felt in the throat and inner ear. A lesion of this nerve is detected by testing the '*gag reflex*'. The patient is asked to open his mouth and the posterior pharyngeal wall is stimulated on one side using a throat swab. A tongue depressor may be used to keep the mouth open. The normal response is a 'gag'. If there is a sensory deficit, the patient may not gag when the affected side is touched.

The Vagus Nerve

The tenth cranial nerve supplies motor innervation from the nucleus ambiguus to most of the muscles of the soft palate, pharynx and larynx. Hence, lesions of this nerve cause dysphagia and dysphonia. The nerve also carries parasympathetic innervation to most of the abdominal structures (except the bladder and rectum which are innervated by the sacral spinal cord). It carries visceral afferents from the pharynx, larynx, esophagus and abdominal organs. Somatic sensation is carried from the

external ear. The vagus nerve travels from the medulla, which is its point of exit from the brainstem, and passes laterally to exit through the jugular foramen along with the ninth and eleventh nerves. It then runs downwards close to the carotid artery. Most of the laryngeal muscles are supplied by a branch called the recurrent laryngeal nerve which loops around the innominate artery on the right and the arch of the aorta on the left. A lesion of the vagus nerve, if unilateral, results in symptoms of hoarseness and a brassy cough. The speech has a hypernasal twang due to difficulty with procuring complete closure of the soft palate. Thus, the word 'egg' may be pronounced as 'engg'. On evaluation of the gag reflex, there is an abnormal movement of the uvula. Because the normal side contracts, the base of the uvula is pulled to the normal side and the tip points towards the affected side. Indirect laryngoscopy will show a decreased movement of the ipsilateral vocal cord. A bilateral lesion will result in dysphagia. There may be nasal regurgitation of fluids. Isolated lesions of the recurrent laryngeal portion of the vagus may be due to an aneurysm of the aorta, an enlarged left atrium and tumours of the mediastinum or thyroid.

The Accessory Nerve

This is the eleventh cranial nerve. It is a pure motor nerve arising from the anterior horn cells in the C1–C5 segments of the cervical spinal cord. However, it is considered a cranial nerve because the rootlets unite and pass upwards into the posterior fossa through the foramen magnum. They then run alongside the vagus to the jugular foramen. The accessory nerve supplies the ipsilateral sternocleidomastoid and trapezius muscles. Clinical evaluation involves having the patient turn the head forcibly against the examiner's hand. The sternocleidomastoid on one side is responsible for turning the face to the opposite side. The trapezius is tested by asking the patient to shrug shoulders against resistance.

The Hypoglossal Nerve

The hypoglossal or twelfth cranial nerve is a pure motor nerve. It arises from the medulla just lateral to the pyramids and leaves the skull through the hypoglossal canal. It supplies all the ipsilateral tongue muscles. To examine the nerve, the patient is asked to protrude her tongue. A lesion of the nerve causes marked atrophy of one half of the tongue. Since the other half is larger and crosses the midline, the tongue appears to protrude towards the affected side. If there is facial paralysis along with the hypoglossal lesion, the position of the tongue can be evaluated with reference to the upper incisors.[1] There will also be fasciculations in the atrophic half of the tongue. Fasciculations should be looked for while the tongue is at rest within the mouth.

MULTIPLE CRANIAL NERVE PALSIES SYNDROMES

Very often cranial nerves are not involved singly but are affected in characteristic patterns. Involvement of multiple cranial nerves on one side suggests a structural lesion (such as a tumour) on the same side. Bilateral involvement suggests a more diffuse process such as basal meningitis[2] and this is particularly likely if the nerves are affected in a patchy distribution rather than in a sequential caudocranial succession. However, bilateral lesions may also be seen with trauma to the base of the skull, or with a tumour arising in the midline such as a nasopharyngeal carcinoma, or a chordoma.

If several cranial nerves are simultaneously affected, the site of the lesion (whether within the brainstem, outside the brainstem and within the skull, or outside the skull in the neck) needs

[1] Because of the facial asymmetry, it may be difficult to evaluate the position of the tongue with reference to the lips.

[2] Causes of this syndrome include tuberculous meningitis, carcinomatous meningitis, sarcoidosis, fungal meningitis, herpes zoster, Wegener's granulomatosis and Behcet's disease. The first two are the most common.

to be determined. Intraparenchymal lesions involving more than one nerve are usually large enough to cause long tract signs resulting in '*crossed hemiplegic*' syndromes. An example of such a lesion is a pontine glioma. Extraparenchymal lesions within the skull present as a few characteristic syndromes which will be discussed below. The syndromes due to a structural lesion in the superior orbital fissure, the parasellar region, the petrous apex and the cerebellopontine angle have been discussed earlier in this chapter. Syndromes involving the lower cranial nerves (X–XII) are summarised here. A tumour such as a glomus jugulare[1] involves the ninth, tenth and eleventh cranial nerves (*Vernet syndrome*). Just below the jugular foramen, the twelfth nerve leaving the hypoglossal canal comes to lie adjacent to these three nerves. A lesion in this location, which is called the posterolaterocondylar space, affects all four of these nerves (*Collet-Sicard syndrome*). As all four nerves pass further down and come to lie behind the parotid gland, they are joined by the cervical sympathetic. A lesion at this location results in ipsilateral ninth to twelfth cranial nerve involvement plus an ipsilateral Horner syndrome (*Villaret syndrome*). Lesions at this site include tumours arising from the parotid gland, the carotid body, the cervical lymph nodes and metastases. In rare cases, tubercular lymphadenitis can cause this syndrome.

[1] Glomus jugulare is a vascular tumour developing in the wall of the jugular bulb.

KEY CONCEPTS

Extraocular muscle paresis

- The sixth cranial nerve (abducens nerve) innervates the lateral rectus while the fourth nerve (trochlear nerve) innervates the superior oblique muscle (LR_6SO_4); all the other recti and the inferior oblique are supplied by the third cranial nerve (oculomotor nerve).
- Paresis of the extraocular muscles results in diplopia. Objects increase in separation in the direction of the affected movement and the image formed by the defectively moving eye is more peripheral.
- Paresis of the third nerve is usually due to compression or due to ischemia (diabetics are expecially prone). Features include ptosis (weakness of levator palpebrae superioris) and diplopia that is worse when the eye is abducted and turned down. A dilated pupil (involvement of pupilloconstrictor fibres) favours a diagnosis of third nerve compression over an ischemic etiology.
- Fourth nerve paresis is usually due to trauma or microvascular ischemia. It results in diplopia that is most severe when looking downwards and inwards; the head is tilted to the opposite side.
- Sixth nerve paresis maybe due to increased intracranial pressure (non-localising), ischemia or a post-viral syndrome. Diplopia is maximum on looking to the side of the paralysis and when the eye is adducted.
- Neuroradiologic investigations (CT/MRI) are vital for investigating paresis of extraocular muscles and the specific treatment depends on the etiology.

Trigeminal neuralgia

- This disorder is characterised by acute brief (seconds to minutes) severe lancinating pain along the distribution of one of the trigeminal divisions (usually maxillary or mandibular).
- Diagnosis is based on history. If sensory or fifth nerve motor deficit is present concomitantly, it is essential to exclude a structural lesion.
- Carbamazepine is generally effective. Alternatives include phenytoin, baclofen and amitriptyline. Surgical approaches are reserved for intractable pain.

Facial nerve palsy

- The causes of seventh nerve paralysis include *Bell's palsy* (thought to be idiopathic; may be related to herpes simplex), geniculate herpes (*Ramsay Hunt syndrom,* vesicles on the ear canal/pinna typical), acoustic neuroma, glomus jugulare tumour (pulsatile tinnitus, mass behind ear drum; IX, X, XII cranial nerve involvement), sphenoid meningioma and sarcoidosis.
- Upper motor neuron lesions (above brainstem nucleus; e.g. a stroke) affect the lower two-thirds of the face on the same side. Lower motor neuron lesions affect the entire face on the same side.
- Clinically, the affected side shows a depressed nasolabial fold and a widened palpebral fissure. The affected eye closes incompletely and globe rotates up (*Bell's phenomenon*). Associated features include hyperacusis, excessive lacrimation and loss of taste.
- Diagnosis is clinical. A CT scan may be obtained if a secondary cause (such as a tumour) is suspected.
- Corticosteroids administered within 48 hours of onset may help Bell's palsy; methyl cellulose eye drops or an eye patch to protect the cornea are important adjunctive measures.

9.11 Diseases of the spinal cord

Anatomy of the spinal cord

The spinal cord is enclosed within a bony covering, the vertebral column. This column is made up of many vertebrae placed end to end. The column is hollow as each vertebra has a central hole known as the *vertebral foramen.* The foramina lying one above the other form the *vertebral canal* which houses the spinal cord. There are 7 cervical, 12 thoracic and 5 lumbar vertebrae, in addition to the sacrum and the coccyx. The vertebral column has an anterior curvature (*lordosis*) in the cervical and lumbar regions, and a posterior curvature (*kyphosis*) in the thoracic region. This shape is optimal for weight-bearing, which is an important function of the vertebral column. Abnormalities in this curvature can alter the space available for the spinal cord. A lateral curvature of the vertebral column (*scoliosis*) is always abnormal.

The vertebrae have two parts—an anterior body which is weight-bearing and a posterior arch. The vertebral bodies are separated from each other by *intervertebral discs* and are held together by anterior and posterior longitudinal ligaments respectively. These discs are relatively avascular structures consisting of an outer fibrous ring (the *annulus fibrosus*) and a central core of soft cartilage (the *nucleus pulposus*). Under excessive pressure the fibrous ring may rupture and the nucleus pulposus may extrude resulting in a ruptured or herniated disc. Commonly, the herniation occurs *lateral* to the posterior longitudinal ligament and results in compression of the *nerve root.* If the posterior longitudinal ligament gives way, a *central* disc herniation may result, causing *spinal* cord compression.

Arising from the vertebral body are two pedicles bearing articular facets (for articulation with the vertebrae above and below) and the pedicles in turn project backwards as the laminae to meet in the midline and project backwards as the spinous process. The pedicles are held together by the *ligamenta flava* (yellow ligaments) and the spinous processes by the supraspinous and interspinous ligaments. All three ligaments are pierced during a lumbar puncture. The intervertebral foramina lie between adjacent pedicles and through them, the nerve roots leave and blood vessels enter the spinal or vertebral canal.

The spinal cord extends from the foramen magnum superiorly to the lower border of the first lumbar vertebra (L1) inferiorly. In younger patients it may extend as far as L2. There is a *cervical enlargement* – a fusiform swelling – in the C5–T1 area; the enlargement is explained by the fact that this areas innervates the upper limbs. Similarly, the *lumbar enlargement* between L1 and S2 innervates the lower limb. Below the lumbar enlargement the cord rapidly narrows. This cone-shaped termination is called the *conus medullaris.*

The meningeal coverings and spaces around the cord are similar to those found around the brain except for two details. Firstly, the epidural space is larger in the vertebral canal than the skull, and secondly, the cord is suspended and

stabilised within the canal by a series of pial thickenings called the *dentate ligaments* extending laterally through the arachnoid upto the dura. Sleeves of meningeal covering extend over the vertebral roots in the intervertebral foramina. Inferiorly, the meningeal coverings extend to cover the intraspinal portions of the nerve roots even after the cord has ended, and finally all three meningeal layers fuse to form a thin cord-like *filum terminale* attached to the coccyx. Between L1 and S2 is a lumbar cistern which is filled with cerebrospinal fluid and through which the nerve roots pass on their way out of the spinal canal. This group of nerve roots is called the *cauda equina* (horse's tail) because of its appearance.

As the fetus develops, the vertebral column grows faster than the spinal cord so that the spinal cord appears to move upwards within the vertebral canal. Hence, cord segments do not correspond exactly to the vertebral levels. In addition, there are eight cervical cord segments but only seven cervical vertebrae. In the cervical region, the cord and vertebral segments correspond. The cervical roots leave through the intervertebral foramen just above the corresponding vertebral level. Thus, the fifth cervical motor root exits through the intervertebral foramina between the fourth and fifth cervical vertebrae. The eighth cervical root exits through the C8–T1 intervertebral foramina. Subsequent roots exit below the corresponding vertebral body. The thoracic cord segments lie one segment above the corresponding vertebral body up to T6, and approximately two segments above between T6 and T12. The lumbar cord segments lie adjacent to the last two thoracic vertebrae and the sacral segments lie adjacent to the first lumbar vertebra. To complicate matters further, below T3, the spinous processes curve downwards so that the horizontal level of the spinous process is one vertebral level below that of the corresponding body. Thus, when speaking of levels in spinal cord pathology it is important to specify if the pathology is at the level of the spinal cord segment, the vertebral body or vertebral spinous process. All levels used in the rest of the chapter will refer (unless specifically stated otherwise) to the cord segments.

Internal anatomy of the spinal cord

A cross-section of the spinal cord shows a central canal, an H-shaped mass of grey matter around it and a large area of white matter around the grey matter. The central canal lies in the transverse limb of the 'H'. It is incompletely bisected by a ventral sulcus and a dorsal septum. The part of the transverse limb anterior to the central canal is called the *anterior commissure* and the part posterior to the central canal is called the *posterior commissure.* The portions of the 'H' anterior to the coronal plane of the anterior commissure constitute the *anterior horns* and the portions posterior to the transverse limb constitute the *posterior horns.* In some parts of the cord (thoracolumbar), there is a small lateral 'bulge' in the middle of the 'H' between the anterior and posterior horns on each side, which is the *lateral horn.* Broadly, the anterior or ventral horn has motor functions (giving rise to the ventral or motor roots of the spinal nerves), the posterior or dorsal horn has sensory functions (receiving the dorsal, sensory roots) and the lateral horn has autonomic functions.

The white matter of the spinal cord is divided into three *funiculi* or columns, the anterior column between the ventral sulcus and the exiting ventral root, a lateral column between the ventral and dorsal roots and a posterior column between the dorsal root and the dorsal midline. Within the white matter are *tracts*, that is, groups of fibres travelling together which have the same type of origin, course, termination and function. The posterior column has the *fasciculus gracilis* medially and the *fasciculus cuneatus* laterally. The former carries ipsilateral touch and deep sensation (pressure, vibration and proprioception) from the T7 level and below; the latter carries similar sensations from above T7. Both tracts terminate in the medullary nuclei (gracile and cuneate nuclei).

The lateral column has the lateral corticospinal tract posteriorly and the spinothalamic tract anteriorly. The fibres in the spinothalamic tract carry pain, touch and temperature sensations from the *contralateral* half of the body since these fibres cross over in the posterior commissure,[1] a few segments above their level of entry. The *somatotopic organisation* within the spinothalamic tract places the sacral fibres outermost and anterior; fibres from progressively higher levels exit from the central grey after crossing over and stack up on the inner surface of this tract. Other spinal tracts are shown in Fig 9.35.

Blood supply to the spinal cord

There are two posterolateral and one anteromedian artery running along the length of the spinal cord. Superiorly an anteromedian vessel, the anterior spinal artery, is formed by branches from the two vertebral arteries. These in turn are fed by a series of segmental spinal arteries. Each spinal artery divides into anterior and posterior branches. The *arteria radicularis magna of Adamkiewicz* arises at the T10 level and may supply the lower two-thirds of the cord. Between the T4–C8 segments is a watershed area, which is especially vulnerable to ischemic injury. Branches from the anteromedian artery supply the ventral two-thirds of the spinal cord.

[1] To be accurate, the pain and temperature fibres end in second-order neurons in the dorsal horn and it is the ascending axons of these second-order neurons that cross over in the posterior commissure.

SPINAL REFLEXES AND SUPRASEGMENTAL CONTROL OF SPINAL REFLEXES — THE BASIS OF SPASTICITY

The term spasticity has been discussed earlier in the section on 'hemiparesis'. It is an involuntary increase in muscle tone which occurs during muscle stretch (that is, when not at rest) and is

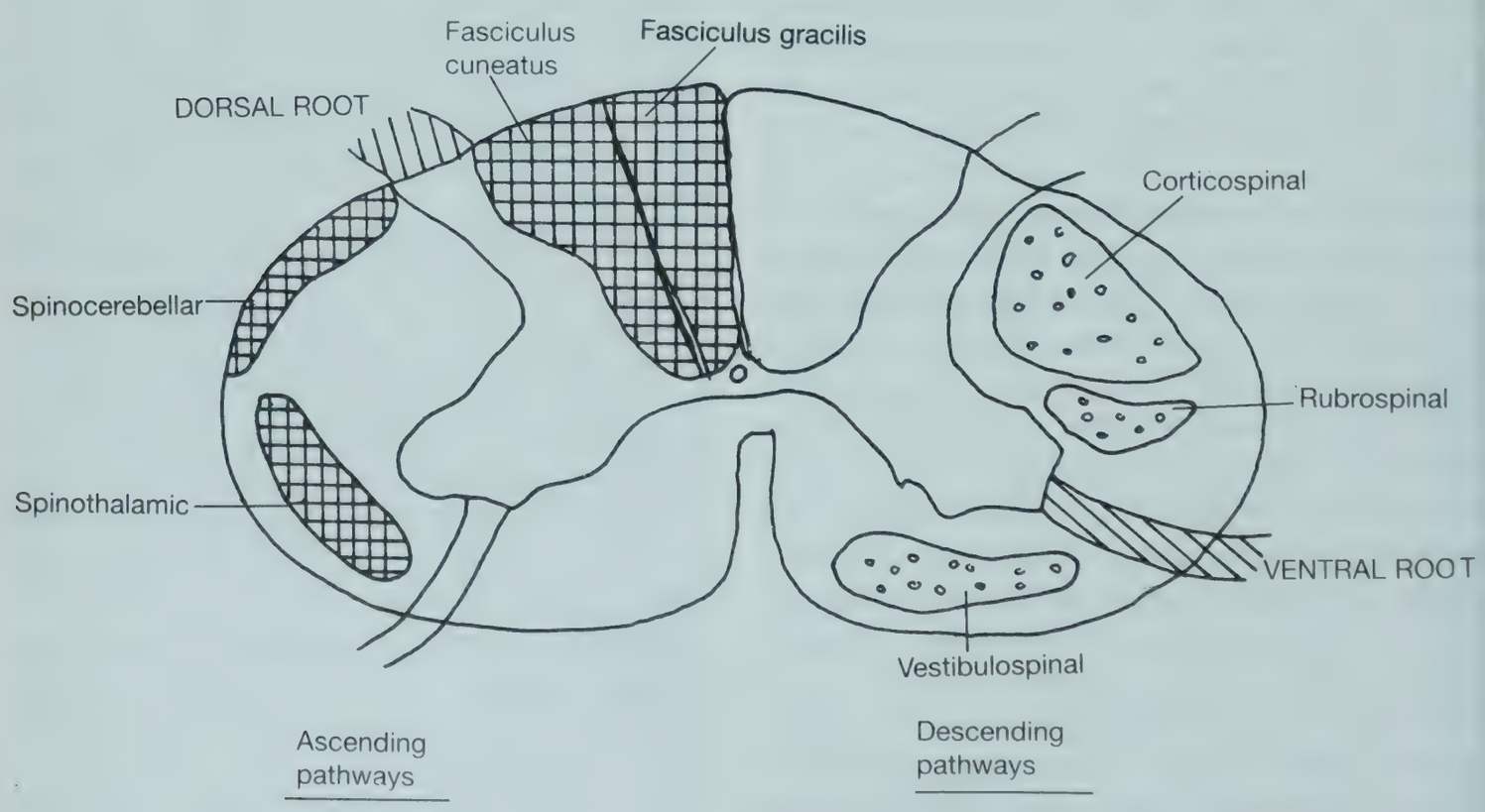


Fig 9.35 Cross-section of the cervical spinal cord showing the major tracts

associated with an extensor plantar response and increased deep tendon reflexes. Muscle tone is due to the spinal segmental reflex arc. Proprioceptive afferent fibres entering the spinal cord divide into a lateral branch, which travels rostrally in the posterior column, and a medial branch which enters the grey matter to constitute the afferent portion of a segmental reflex arc. The fibres may directly synapse on an alpha motor neuron to form a monosynaptic synapse. Such monosynaptic reflex arcs are typically formed by afferent fibres from the muscle spindle which detect muscle stretch and provide excitatory feedback to the alpha motor neuron of the same muscle causing its contraction. This reflex arc is normally dampened by descending inhibitory input from the corticospinal tract. Other descending tracts (reticulospinal, vestibulospinal and rubrospinal) increase the sensitivity of the reflex arc.[1] The reflex arc is also dampened by recurrent or *Renshaw cell* inhibition,[2] presynaptic inhibition and inhibitory input from the Golgi tendon organs in the same muscle (activated once the stretch is 'too much'), as well as the muscle spindle afferent fibres in antagonistic muscles (reciprocal inhibition). In spinal spasticity, presynaptic inhibition (GABA-mediated) and reciprocal inhibition (glycine-mediated) are diminished. Cutaneous sensory afferent fibres (such as pain) facilitate the reflex arc. The involvement of these various pathways and neurotransmitters explains why strychnine and tetanus toxin (glycine antagonists) cause increased spasticity, while benzodiazepines and baclofen (GABA agonists) and morphine (opioid pain reliever) decrease spasticity. Spasticity may sometimes be beneficial, for instance it may enable a patient to use a weak limb like a stiff crutch. It may also cause painful flexor spasms especially at night, and in bedridden patients create difficulties in catheterisation of the bladder and maintenance of perineal hygiene.

[1] Hence, an incomplete transection of the spinal cord may cause more spasticity than a complete transection.

[2] Collaterals from the muscle spindle afferent fibres excite a cell called the *Renshaw cell* which then inhibits the alpha motor neuron.

CLINICAL SYNDROMES IN SPINAL CORD LESIONS

Transverse Spinal Cord Lesions and Localisation of a Spinal Level

Transverse cord lesions disrupt spinal cord function at one or more adjacent horizontal levels involving numerous contiguous portions of the cord at that horizontal level on both sides. If all the neurons and tracts at the given level are affected, it is called a *complete transection of the cord.* Otherwise, it is called an incomplete or partial transection of the cord. The spinal cord level at which evidence of root involvement or lower motor neuron involvement is present is most likely the anatomical site of the lesion. Suggestive symptoms and signs include root pain, persistent flaccid paralysis, wasting and fasciculations of the muscles supplied from that segment, absence of a tendon reflex localisable to that segment or a dermatomal pattern of sensory impairment with normal sensation in adjacent dermatomes above and below that level.

The other findings in complete transection of the cervical or thoracic spinal cord are complete paralysis of all four limbs (quadriplegia) with a lesion between the craniovertebral junction and C5, and complete paralysis of both lower limbs (paraplegia) with a lesion between T2 and T12. Lesions between C5 and T2 will paralyse some of the upper limb musculature and also cause paraplegia. In the case of incomplete cord transection at these levels, there is a weakness (paresis) rather than complete loss of motor function (plegia). Thus, there would be quadriparesis or paraparesis rather than quadriplegia or paraplegia.

In case of a complete transection of the spinal cord which is of acute onset (for instance, following a trauma to the spine or a spinal

infarct), there is initially a complete loss of muscle tone below the lesion. This is called the stage of *spinal shock*. After days to weeks, the muscle tone gradually returns with tone being initially higher in the antigravity muscles (*paraplegia in extension*). Ultimately, tone is increased to a greater extent in the flexor muscles and there are flexor spasms. Later there are flexion contractures (*paraplegia in flexion*). The spinal cord level below which there is weakness and a change in tone is called the *motor level.* A guide to localisation of the motor level is given in Table 9.33.

Loss of sensation occurs below a certain level. The sensory level as recorded is often well below the site of the lesion, specially in an incomplete transection of the cord. This is due to two factors. Due to lamination of fibres in the ascending spinothalamic tract, the pain sensory fibres from the lower regions, which are

Table 9.33 Guide to the localisation of motor deficits

Joint	*Movement*	*Segmental level*			*Nerve*	*Muscles*
Shoulder	adduction, flexion	C5,6			brachial plexus	pectoralis, subscapularis
	abduction	C5,6			suprascapular, axillary	30° supraspinatus, later deltoid
	extension		C6–C8		thoracodorsal	Lattisimus dorsi
	external rotation	C5,6			brachial plexus	subscapularis
Elbow	flexion	C5,6			musculocutaneous	biceps, brachialis
	extension		C6–C8		radial	triceps
Forearm	pronation		C6–C7		median	pronator teres
	supination		C6–C7		posterior interosseous (branch of radial)	supinator
Wrist	extension		C7–C8		posterior interrosseous	extensor carpii
	flexion		C6–7		median and ulnar	flexor carpii
Thumb	extension, abduction		C7–8		posterior interosseous	extensor and abductor pollicis
	other movements			C8,T1	median	thenar muscles
Fingers				C8,T1	ulnar	intrinsic and hypothenar muscles
Hip	flexion	L1–L3			femoral	Iliopsoas, sartorius
	extension			L5–S2	inferior gluteal	gluteus maximus
	adduction	L2–L4			obturator	adductors
	abduction		L4–S1		superior gluteal	gluteus medius
Knee	extension	L2–L4			femoral	quadriceps femoris
	flexion			L5–S2	sciatic	hamstrings
Ankle	dorsiflexion		L4–S1		deep peroneal	anterior tibial
	plantar flexion			S1–S2	tibial	gastrosoleus
Foot	inversion		L4–L5		tibial	posterior tibial
	eversion			L5–S1	superficial peroneal	peroneii

relatively more superficial, may be involved, while deeper fibres entering at higher levels may be spared. Similarly a posterior midline lesion may involve the 'leg fibres' in the fasciculus gracilis but not the 'trunk fibres' more laterally. Also, there is a typical gradation of sensory impairment from anesthesia to partial sensory impairment to normal sensation. If the level is defined as the point where the patient is first able to feel the stimulus rather than the point at which there is normal perception, a wrong level may be obtained. A more correct sensory level can be obtained by recording the level of transition from impaired to normal sensation, and by assessing the sensory level for vibration and touch as well as for pinpricks. Vibration may be assessed over the spinous processes. Sensation is best tested by starting within the abnormal area and moving the stimulus outwards, but also by taking care to compare the stimulus intensity with a clearly normal area. Occasionally, one finds a hyperalgesic border zone of sensory disturbance just above the level of sensory impairment. In case of complete transection of the spinal cord all sensory modalities are affected. In partial lesions, there may be separate areas of impairment for 'posterior column sensations' (vibration, pressure, joint position sense) and 'spinothalamic sensations' (pain and temperature). Analysis of this difference may help us localise the area within the cord (at a given level) which are involved by the pathological process. The sensory level may be determined with reference to Fig 9.36 showing the dermatomal distribution of sensory perception. It should be recalled that the sensory nerves to the trunk slope downwards as they pass anteriorly.

The reflex level is the level above which reflexes are normal and below which reflexes are either lost (in the stage of spinal shock) or exaggerated (spastic paraplegia). The segmental level for each reflex is as follows:

Segmental level of various deep tendon reflexes

Reflex	*Segmental level*
Biceps	C5
Triceps	C7
Supinator	C5,6
Knee	L3,4
Ankle	S1

Disturbances of vasomotor function and sweating occur below the lesion (*autonomic level*) due to disruption of the central sympathetic fibres descending in the lateral columns. This trophic disturbance combined with sensory impairment and the patient's inability to change posture (so as to relieve pressure at any one spot), makes the patient susceptible to the development of *pressure sores* or *decubitus ulcers.* There is also a paralysis of bladder and rectal function, and sexual disturbances occur.

The level of a lesion will usually be at or above the highest noted motor, sensory, reflex or autonomic level or at the level showing evidence of root or anterior horn cell involvement (segmental level).

Hemitransection of the cord (Brown-Sequard syndrome)

The clinical characteristics of the Brown-Sequard syndrome can be understood by reviewing the motor and sensory pathways and Fig 9.36 showing a transverse section through the spinal cord. There is *ipsilateral spastic paresis* with hyperreflexia and pyramidal signs below the lesion due to involvement of the lateral corticospinal tract. There is also an *ipsilateral impairment of vibration and position sense* and of tactile discrimination due to lesions of the posterior columns. Touch may be preserved since fibres also ascend in the contralateral spinothalamic tract. There is *contralateral impairment of pain and temperature sensation* which ascend in the crossed lateral spinothalamic tract. There may initially be ipsilateral

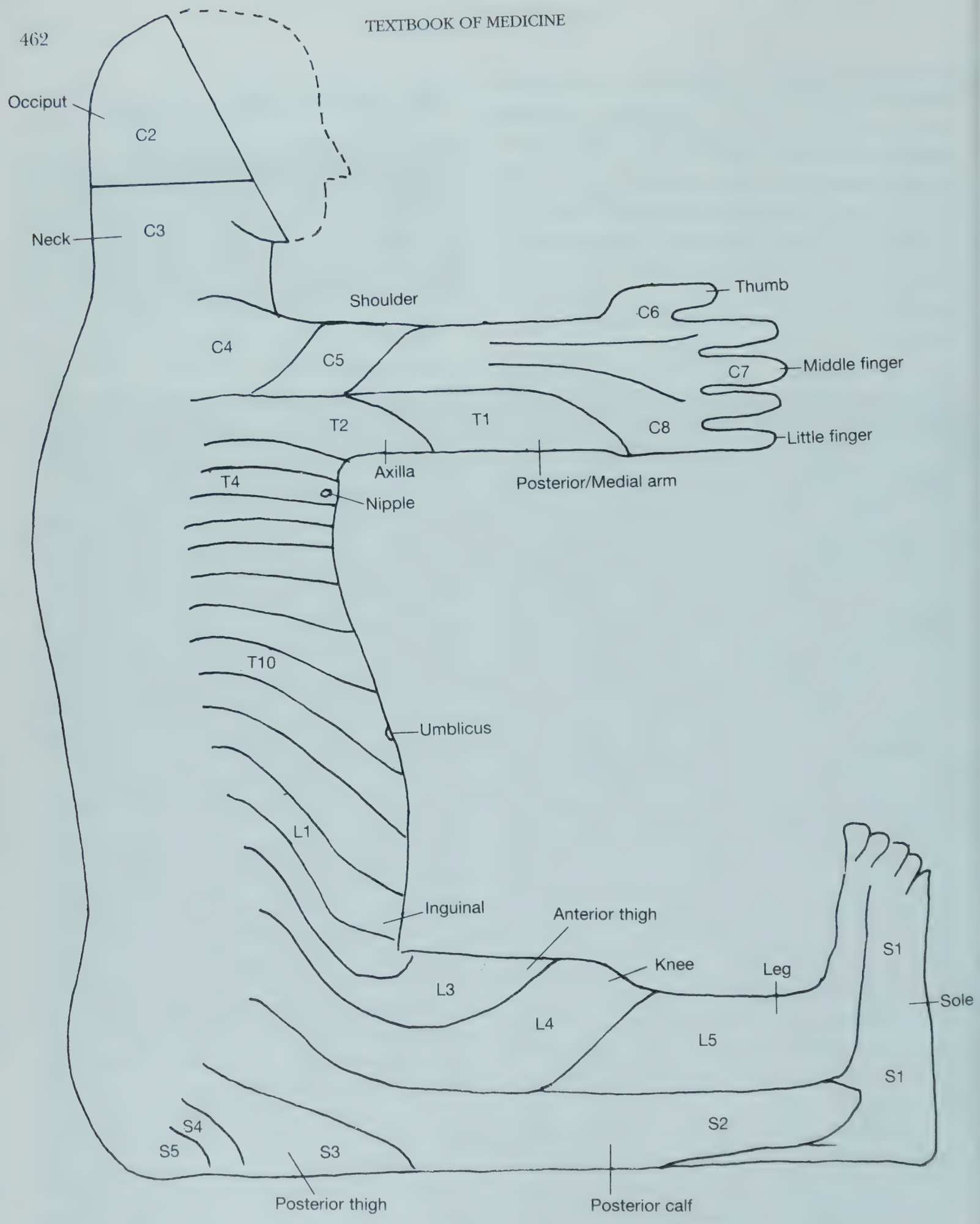


Fig 9.36 Schematic representation of the sensory dermatomes

vasodilatation with hyperemia and hyperesthesia and later there may be hypothermia and cyanosis of the affected area due to ipsilateral involvement of descending sympathetic fibres. Complete Brown-Sequard syndromes are very rare. Trauma and extramedullary compressive lesions frequently cause a partial Brown-Sequard syndrome.

Lesions of the conus medullaris and cauda equina

The portion of the spinal cord containing the spinal segments L4–S2 is called the *epiconus*. The portion containing the terminal spinal cord segments (S3 and below) constitutes the conus. Sometimes, lesions involving both areas are collectively described as lesions of the *conus medullaris*. The cauda equina consists of those spinal roots whose point of emergence from the spinal cord is below the tip of the conus medullaris – spinal roots L3 to S5. Involvement of the epiconus is characterised by lower limb weakness involving hip extension, knee flexion and movements of the foot and toes; absent ankle jerk (with preserved knee jerk); sensory impairment below L4 and bladder dysfunction of a spastic type. Involvement of the conus results in saddle anesthesia[1] a flaccid bladder (with overflow incontinence), loss of anal sphincteric tone and absence of anal[2] and bulbocavernosus reflexes. An isolated conus lesion will not cause lower limb weakness.

The distinction between the clinical presentation of a lateral, extramedullary lesion (also called a cauda equina syndrome) and a midline, intramedullary lesion (also called a conus medullaris syndrome) is described in Table 9.34. It is important not to miss diagnosing lesions in this portion of the spinal cord. A lesion is often missed if careful examination of genital and perineal area and sphincteric tone is not undertaken. It is relatively less important to make a clinical distinction between a cauda equina type and conus medullaris type of lesion. Often a mixed pattern is seen. Symptoms suggestive of conus medullaris involvement suggest that the lesion can only be within the bony vertebral canal whereas the differential diagnosis of a pure 'cauda equina' syndrome includes a lesion in the lumbar plexus.

Types of pain in a spinal cord lesion

Root pain is caused by injury to a nerve root, usually either by compression or stretching. It begins at the spinal level and extends distally along the dermatomal distribution of the root as a sharp, severe pain. Root pain is least severe in positions that minimise the mechanical pressure on the root. It is typically worsened by coughing, sneezing or straining at stool, all maneuvers that increase the intraspinal pressure.

Funicular pain is due to compression of the long tracts within the spinal cord. It is typically a diffuse, dull ache involving an entire extremity. It may be worsened by movements that stretch the cord such as neck flexion.

Bladder involvement in spinal cord lesions as well as other types of neurological lesions is discussed in the section on 'neurogenic bladder' in the Renal Diseases chapter.

SPINAL CORD COMPRESSION

Etiology Any spinal cord lesion which can be localised to a particular level should be considered secondary to a compression of the cord until proved otherwise. This is because many of the causes of compressive myelopathy are treatable, but, if unrecognised, can rapidly progress to irreversible paraplegia, with loss of bladder function and sensation. Spinal cord compression is classified according to the location of the compressing lesion as being *either extradural* or intradural but *extramedullary* (outside the substance of the spinal cord). Most causes of spinal cord compression are extradural.

[1] This is the part of the body that would come in contact with a saddle if one were riding.

[2] Stroking of the perianal skin results in reflex contraction of the anal ring.

Table 9.34

Conus medullaris syndrome	*Cauda equina syndrome*
More likely to present with bilateral signs since the conus is compact	More likely unilateral at onset
Isolated conus lesions cause no lower limb weakness; if concomitant nerve root involvement occurs, L3 which lies close to the tip of the conus is most often affected—weak quadriceps, L3 hyperalgesia	Typically, there is unilateral lower limb weakness involving feet and toes
Saddle anesthesia seen early without weakness or anesthesia elsewhere	Saddle anesthesia seen late with bilateral lower limb weakness, sensory findings
Absent anal reflex, bladder involvement early	Rare, late
Aching low back pain	Root pain radiating into legs

Clinical features The clinical picture of cord compression may be a partial Brown-Sequard syndrome that worsens to a complete transection of the cord. The urgency is to arrest this process since deficits once established may be irreversible. A very early lesion may resemble a polyneuropathy, with paresthesiae in the feet and a stocking pattern of sensory impairment. Brisk deep tendon reflexes or an extensor plantar response suggest the correct diagnosis. The clinical symptoms in an extramedullary lesion and an intramedullary lesion are compared below.

Extramedullary lesion	*Intramedullary lesion*
Root pain or midline back pain	Funicular pain
Brown-Sequard syndrome	Dissociated anesthesia (discussed later)
Early corticospinal signs	Late and less prominent
Early loss of sacral sensation	Sacral sparing
CSF abnormal	CSF more likely to be normal

These rules should be considered statistical approximations and cannot definitively establish the site of the lesion.

Investigations

Myelography: An intramedullary tumour causes a fusiform enlargement of the cord. Often obstruction is incomplete. When complete obstruction supervenes there is a deep U-shaped meniscus at the upper end of the column of dye due to the gradual sloping profile of the obstructing enlargement. An extradural, intramedullary lesion typically begins laterally. As it enlarges, it widens the ipsilateral thecal space and narrows the contralateral thecal space. There is a triangular area of thecal enlargement just below the tumour. When complete obstruction supervenes, the upper margin of the column of dye is a well-defined shallow meniscus– 'cap sign'. In extradural compression, there is a displacement but no widening of either the ipsilateral or contralateral thecal space. With complete obstruction there is an ill-defined or feathered margin of contrast. There may be an erosive or sclerotic lesion in the adjacent bone.

The individual causes of spinal cord compression are tabulated below (Table 9.35).

Tumours of the Spinal Cord (Compressive)

Tumours causing spinal cord compression may be extradural, in which case they are most often metastatic (from prostate, lung, breast, lymphoma and myeloma), or intradural, when they are likely to be primary (neurofibroma, meningioma). The initial symptom is local back

Table 9.35 Causes of cord compression

Etiology	*Clinical clues*
Intervertebral disc protrusion	commonest in the lumbar region (discussed under low back pain) or cervical; less common in thoracic cord
Local primary tumours	usually intradural extramedullary; e.g. neurofibroma/meningioma
Metastatic deposits	prostate, breast, lung cancers, lymphoma, myeloma; root pain, local tenderness, bone erosion on X-ray; positive bone scan
Tuberculosis	fever, cough, history of tuberculosis, abnormal chest X-ray; myeloradiculopathy; laminae may be involved in bony destruction
Epidural abscess	history of minor local trauma; may have septic focus; root pains, fever, neck stiffness
Epidural hemorrhage	trauma (including lumbar puncture) or coagulopathy
Extramedullary hematopoiesis	anemia, hepatosplenomegaly, facial dysmorphism; history of hematologic disorder
Aortic aneurysms	pulsatile abdominal mass, abdominal bruit, may have abnormal lower limb pulses
Atlantoaxial dislocation	discussed under craniovertebral anomalies
Endemic fluorosis	mottled teeth, ossified interosseous membrane, osteophytic bar compresses cord anteriorly; root pain; endemic in south India

pain, which is worse at night. This is followed by root pain and other symptoms of a compressive cord lesion. There is focal tenderness and a plain X-ray may show osteolysis, osteoblastic changes or a compression fracture. Bone scans may be more sensitive and can detect additional, clinically-silent lesions. A sagittal view MRI, a myelogram, or a CT scan (if there is an adequate clinically localisable level), will also show the lesion. The investigation of choice to confirm the diagnosis is a myelogram or an MRI, whichever can be done more rapidly.

If an extradural tumour is detected, an immediate bolus of dexamethasone (10 mg intravenous) is given to reduce cord swelling and is continued every six hours until the compression is relieved. Surgery (decompressive laminectomy, with or without tumour resection) is the treatment of choice. If the tumour is in the vertebral body, an anterior approach may be required. If the patient has multiple levels of compression by the tumour, is in poor general health, has been totally paraplegic with a dense sensory level for more than 48 hours, is known to have a highly radiosensitive tumour, or is diagnosed at the stage of back pain before the onset of neurologic signs and symptoms, radiotherapy is preferred. 3000 rads are given in a rapid, fractionated fashion over 3 to 5 days. Improvement is seen within 48 hours. An intradural tumour usually evolves more slowly and definitive surgical resection is possible.

Spinal epidural abscess

A spinal epidural abscess is another type of spinal cord compression which should not be missed since a delay in diagnosis can lead to paraparesis or death. The typical setting is a patient who has a minor focus of infection and sustains a minor back injury. Symptoms begin with fever, and mild back pain and spinal

tenderness. After a few days there are root pains, headache, neck stiffness (with normal sensorium) and cord compression develops, which can progress with remarkable rapidity. The causative organism is usually Staphylococcus aureus. A tuberculous abscess may rarely present in this fashion. The site of the abscess is usually thoracic but may be cervical or lumbar. An X-ray of the spine is very often normal. A myelogram (with a cisternal puncture[1]) or an MRI should be obtained, again selecting the modality which is most rapidly accessible. Treatment consists of immediate decompressive laminectomy, and drainage of the abscess followed by high dose intravenous antibiotics.

Epidural or subdural hemorrhage

This presents as acute onset severe pain in the back and along the distribution of multiple roots. Causes include a coagulopathy, minor trauma, and bleeding from a tumour or arteriovenous malformations. An MRI is more sensitive than a CT scan in this situation. The treatment is surgical drainage.

Herniated intervertebral disc

A herniation of the intervertebral disc, specifically of the nucleus pulposus, typically presents as an acute onset back pain while the patient is lifting something with the spine flexed. The most common site is the L5–S1 intervertebral disc followed by other lumbar and cervical discs. A thoracic disc prolapse is rare. The symptoms include root pain, loss of normal curvature of spine, pain on movement of spine and spasm of the paraspinal musculature. Usually, the herniation is lateral and impinges more on the root than the spinal cord. A central disc herniation can cause a myelopathy or a cauda equina syndrome. An X-ray of the spine may show a narrowing of the intervertebral space but a CT, myelogram or MRI are more useful. Management consists of rest and antiinflammatory agents followed in 1–2 weeks by a programme of graded muscle strengthening exercises. A 'back brace' or girdle may weaken the paraspinal muscles and may be harmful. Epidural steroids provide short term relief but may cause local scarring. The indications for surgery are severe pain, progressive worsening of motor weakness and bladder involvement. The disc is removed through a laminotomy or a laminectomy.

Cervical spondylotic myelopathy

Cervical spondylotic myelopathy typically affects elderly individuals in whom it presents as a gait disorder with brisk tendon reflexes, extensor plantar responses and abnormal vibration perception. Clinical differentiation from a subacute combined degeneration due to vitamin B_{12} deficiency may be difficult. The patient walks stiffly, with a broad base and may have mild flexion at the knees. There may be a spastic bladder and signs or symptoms of cervical root involvement (usually C5 or C6 root). An X-ray of the cervical spine shows a loss of cervical lordosis, narrowing of the intervertebral spaces, mild subluxations at one or more levels, and a spondylotic bar joining adjacent vertebral bodies along their posterior margin. There may be calcification in the posterior longitudinal ligament. The diameter of the vertebral canal is normally greater than 15 mm, but in thes patients becomes less than 11 mm, or 7 mm during extension of the neck. Somatosensory evoked potentials localise the abnormality to the cervical cord. Treatment involves rest, a cervical collar, traction, and physical therapy (in the form of gait training) to maintain mobility. With bladder involvement or rapid worsening of gait, surgical decompression is indicated.

Lumbar canal stenosis is discussed in the section on low back pain and compression at the craniovertebral junction is discussed in the section on congenital abnormalities of the nervous system.

[1] A lumbar puncture may carry the infection into the subarachnoid space causing meningitis.

NON-COMPRESSIVE MYELOPATHIES

Once spinal cord compression has been excluded, a variety of causes for non-compressive myelopathy need to be considered. In upto 40 per cent of patients with a non-compressive myelopathy the clinical presentation suggests a transverse myelitis but no specific etiology can be identified. The syndrome develops over a period ranging from 1 day to 2 weeks. There may be associated back pain. Examination of the CSF may show 5–50 lymphocytes/mm^3. Spontaneous recovery can occur and the degree of recovery is greatest in patients with slowly developing partial lesions. About 20 per cent later develop mutiple sclerosis. Conversely, a patient with multiple sclerosis may present with transverse myelitis. In a few patients there is associated optic neuritis or the myelitis occurs as part of a postviral demyelination.

Infections which present with myelitis may be viral or bacterial (tuberculosis, syphilis). These are discussed in the chapter on infections. A toxic myelitis may be seen in lathyrism and with some drugs. Lathyrism has been discussed in the section on nutritional disorders. Iodochlor-hydroxy-quinoline (enteroquinol) has been suspected to cause myelopathy with optic neuritis.

There are several vascular lesions which may cause myelitis. There may be embolic infarcts affecting the watershed area of the spinal cord. Besides atheromatous emboli, a minor trauma may be followed by embolisation of the nucleus pulposus presenting as an acute transverse myelitis. A special type of infarct is the *anterior spinal artery syndrome*. The anterior spinal artery supplies the anterior two-thirds of the spinal cord. In this syndrome, there is loss of all sensory modalities at the level of the lesion and motor weakness associated with pain and temperature impairment below this level. Proprioceptive fibres within the dorsal columns are spared. A spinal arteriovenous malformation can cause myelitis due to ischemic steal, or hemorrhage into the cord. Progression may be gradual or 'stuttering'. There may be claudication-like pain in the legs. A bruit may be heard over the spine overlying the lesion. An imaging study will detect most lesions but selective spinal angiography is the gold standard and is done preoperatively.

A vitamin B_{12} deficiency causes a syndrome of *subacute combined degeneration,* so called because of the involvement of the posterior and lateral funiculi. There is spastic ataxia along with a peripheral neuropathy (extensor plantar and absent ankle jerks[1]). Other features of vitamin B_{12} deficiency are discussed in the section on blood diseases.

Intramedullary tumours can also present as non-compressive myelopathy. Sixty per cent of these tumours are ependymomas which arise from the filum terminale and present as a conus medullaris syndrome. Twenty-five per cent of these tumours are astrocytomas; these may be associated with intramedullary cavitation.

Spinal arachnoiditis presents as scarring affecting multiple spinal roots bilaterally. This syndrome almost invariably occurs only in patients who have had multiple myelograms and surgeries on their back. There may be transient elevation of proteins and cell counts in the CSF. Laminectomy has been tried but there is really no effective treatment and many patients become dependent on analgesics.

In a patient who is known to have a malignancy and presents with myelitis, spinal cord compression is by far the most likely cause. However, if spinal cord compression is ruled out, other causes include intramedullary metastases (common with melanomas), radiation myelitis, carcinomatous meningitis (presenting as a cauda equina syndrome associated with headache), and in rare cases, a paraneoplastic necrotising myelopathy.

[1] Other causes of absent knee jerk with extensor plantar responses include tabes dorsalis, Friedreich's ataxia, and HIV-associated myelopathy.

SYRINGOMYELIA

Syringomyelia is a syndrome characterised by the formation of a cavity within the spinal cord. The broadest part of the cavity, which is typically long and narrow, lies in the cervical spinal cord. The cavity can extend downwards into the lumbar segments and upwards into the brainstem; the latter condition is called *syringobulbia*. The cavity typically communicates with the central canal at one or more levels. Bony anomalies of the vertebral column are frequently associated: flattening of the base of the skull,[1] fusion of cervical vertebrae (*Klippel-Feil anomaly*) and dorsal scoliosis. Most patients with syringomyelia show herniation of the cerebellar tonsils through the foramen magnum (*Arnold-Chiari malformation*). The etiopathogenesis is unclear in most cases of syringomyelia. In a small percentage, the cavity (*syrinx*) is secondary to an intramedullary spinal cord tumour, or bleed.

Clinical features The clinical picture is characteristic but not pathognomonic. The clinical syndrome is the consequence of a very slow-growing, space-occupying structure within the cervical spinal cord. Other characteristic features are a consequence of the central location and the ability to extend asymmetrically into both halves of the spinal cord.

Symptoms typically begin insidiously in adult life. There is segmental sensory impairment in the distribution of the cervical dermatomes. This involves both the upper limbs and may extend upwards into the neck and downwards over the thorax. Since sensory perception is intact above and below the level of the lesion, this pattern is described as suspended sensory loss and the area affected is described as a 'cape distribution' (Fig 9.37). A characteristic feature is that within the area of sensory deficit, the pain and temperature fibres (that cross over to the opposite side of the spinal cord at the level of entry) are disrupted by the syrinx, leaving the perception of touch and pressure relatively intact; this pattern is called *dissociated sensory loss*.

Patients with syringomyelia will also develop lower motor neuron signs in the upper limbs (wasting, weakness and fasciculations). These may begin in the small muscles of the hands. There is marked wasting, weakness and fasciculations in the affected muscles. Deep tendon reflexes are usually lost. There may be a Horner syndrome, and a funicular-type of pain is common.

In the lower limbs there may initially be very minimal upper motor neuron signs such as, an extensor plantar response. Later, there is spastic paraparesis with ataxia due to loss of posterior column sensations. Bladder involvement is rare. Kyphoscoliosis may be seen. All features may be asymmetrical, but exclusively unilateral signs are extremely unusual. Bulbar involvement usually affects the medullary tegmentum and the symptoms are dysarthria (twelfth nerve), dysphagia (tenth nerve), wasting and weakness of the trapezius and sternocleidomastoid (eleventh nerve), dissociated anesthesia over the face (spinal tract of the trigeminal) and nystagmus.

Investigations In many patients the clinical features are very characteristic and the only differential diagnosis is between a syringomyelia and an intramedullary tumour. MRI demonstrates the syrinx well, and with gadolinium-enhancement will reliably detect an associated intramedullary tumour, if one is present. A CT myelogram with delayed pictures is also capable of demonstrating the syrinx.

Treatment The course of the illness is very slow, as well as erratic, with long periods during which there is no worsening. In such patients, treatment should be restricted to the use of physiotherapy and orthotic devices. In patients in whom there is a progression in disease, a variety of surgical procedures have been

[1] Platybasia

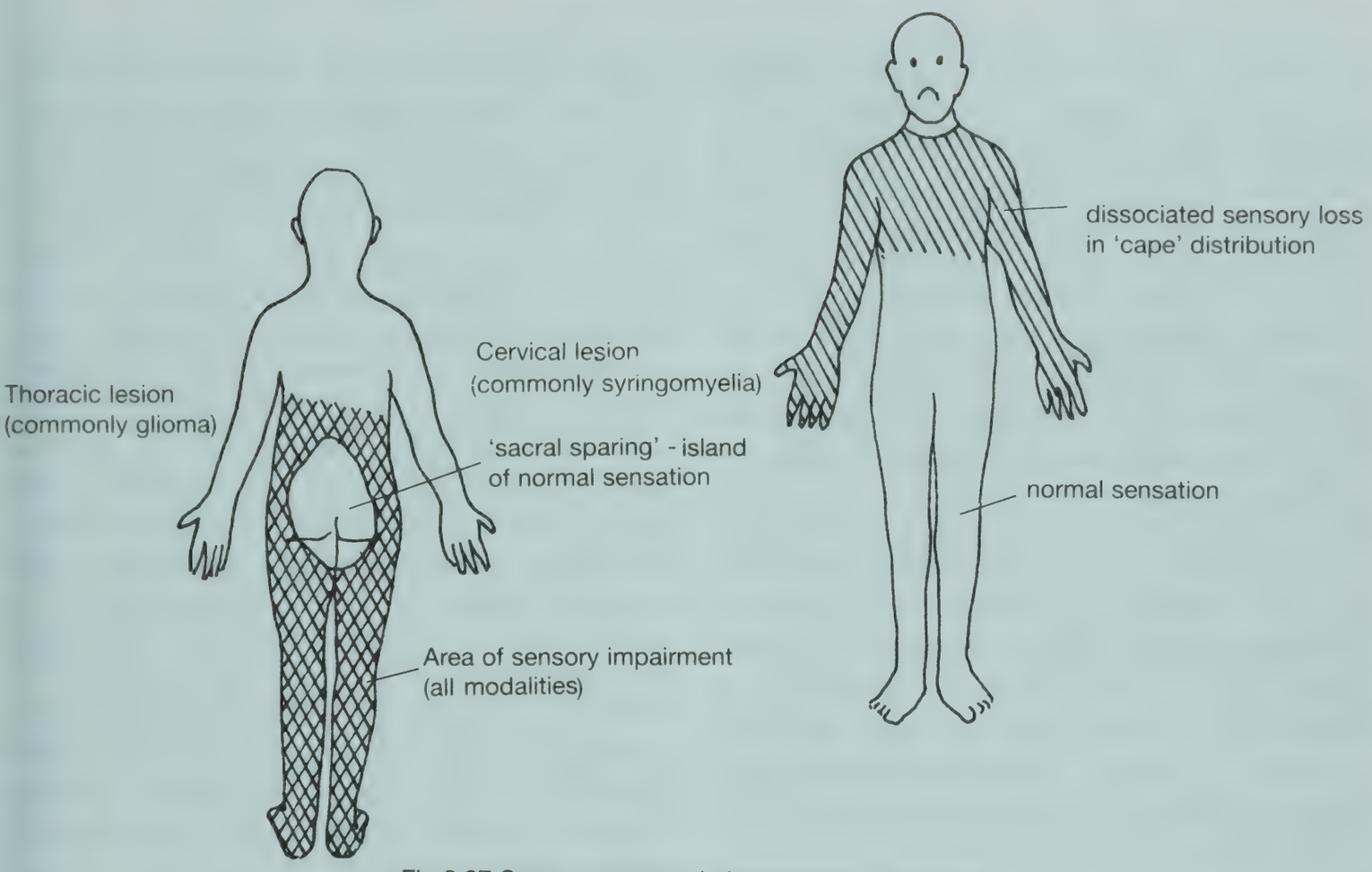


Fig 9.37 Sensory patterns in intramedullary lesions

attempted in an effort to stop further progression. Laminectomies and suboccipital decompression, shunting of the syrinx (syringostomy) and plugging of the obex[1] are some of these techniques.

Spinal cord trauma

The commonest cause of spinal cord injury is trauma. The damage is due to fracture or dislocation of a vertebra. The commonest causes are motor vehicle accidents and fall from a height.

Pathology There may be a vertebral fracture and compression, or the impact of the trauma may itself cause injury to axons and blood vessels. Immediately after the injury there is white matter edema and grey matter hemorrhage. In the first four hours (perhaps eight) some of this tissue is still salvageable. Thereafter, there is ischemic infarction. A late complication is cavitation of the infarcted cord. The cavity may expand causing a progressive syringomyelic syndrome.

Management The first principle is to avoid further injury. In patients with head injury the cervical spine should be immobilised during transport and until clinical (and if indicated, radiological) examination has excluded a cervical cord lesion. Life-support measures are initiated. If intubation is required in a patient with a suspected cervical cord injury, blind nasotracheal intubation is safer than extending the neck to attempt conventional endotracheal intubation. Patients with cervical cord lesions may be hypotensive due to loss of sympathetic tone and will need intravenous fluids to maintain blood pressure.

The clinical evaluation should assess motor power, sensations and reflexes over the trunk

[1] This is based on the theory that the transmission of normal CSF pressure waves into the syrinx results in its expansion.

and limbs. In an unconscious patient reflexes and tone are assessed. The findings will be similar to that described for an incomplete or complete transverse myelopathy. In the acute stage, tone and reflexes are diminished (*stage of spinal shock*). A specific syndrome in patients with a preexisting narrow cervical canal and a relatively minor superimposed injury is the *central cord syndrome.* The upper limbs are weak and there is an impairment of pain and temperature sensations, but the trunk and lower limbs are normal. This is due to pericapillary hemorrhages in the central grey affecting crossing fibres and adjacent corticospinal fibres to the cervical area while sparing more peripheral sensory and motor fibres to the lower limbs. If a cord lesion is suspected on examination, imaging of the spine will help confirm the diagnosis and determine the extent of the cord injury. The clinical examination helps decide the area to be imaged. If there is a vertebral fracture or dislocation this should be surgically corrected, usually by a neurosurgeon, as soon as possible. Intravenous methylprednisolone given within 4 hours may improve the ultimate degree of recovery in patients with traumatic cord injury, with or without a vertebral fracture. Naloxone, Thyrotropin-releasing hormone and GM2 ganglioside are diverse agents being evaluated for possible therapeutic benefit in the early posttraumatic period.

Care of a Patient with a Spinal Cord Lesion

The first priority is to confirm that the patient with para- or quadriparesis does indeed have a lesion in the spinal cord; only then should it be identified and treated, if possible. Alternative causes of paraplegia include an anterior cerebral artery infarct, parasagittal tumour, and hydrocephalus, none of which cause significant sensory loss. Peripheral neuromuscular causes of lower limb weakness must also be distinguished. Quadriparesis must be differentiated from bilateral strokes causing bilateral hemiplegia. The latter group of patients often have a history of two episodes, greater upper limb weakness and an emotional lability called pseudobulbar palsy ('laughing and crying inappropriately'). Again, neuromuscular causes such as periodic paralysis or a Guillain-Barre syndrome must be excluded. The supportive care of the patient may be discussed under two headings: immediate care and long term care. Immediate care focuses on respiratory support in patients with cervical cord injury. If the forced vital capacity is less than 12 ml/kg or if there is arterial hypoxemia, ventilatory assistance should be provided. All patients should have chest physiotherapy to prevent atelectasis and pneumonia. There may be cardiovascular instability which should be treated appropriately. Pulmonary thromboembolism, stress ulcers and ileus are acute complications for which prophylactic therapy may be indicated. Immediate physiotherapy involves splinting of limbs and passive exercises to prevent contractures (such as a foot drop). Long term care focuses on prevention of secondary damage to the urinary tract since renal failure is a common cause of premature death in these patients. Bladder care should include attention to prompt treatment of urinary tract infections; intermittent catheterisation is preferable to indwelling catheters. Decubitus ulcers should be prevented by frequent repositioning and paying attention to skin care. Prevention of constipation, long term respiratory support, if required, treatment of depression and psychosocial support are useful adjunctive measures. If the patient has a problem due to spasticity (painful flexor spasms or adductor spasms interfering with perineal hygiene), there are several therapeutic options. These include reducing afferent input to the reflex arc (treat infections, skin ulcers, pain), passive stretch, oral or intrathecal baclofen, or injection of botulinum toxin into the adductor muscles. Diazepam is not very effective.

KEY CONCEPTS

Localisation in spinal cord disease

- Since the spinal cord is shorter than the vertebral column, spinal levels may not correspond to vertebral levels.
- Lesions at or above C4–C5 cause quadriparesis, bladder disturbances, and diaphragmatic weakness. Lesions at C5–C6 spare arm flexion and abduction; lower motor neuron signs in the upper extremity (weakness of biceps, deltoid, latissimus dorsi; absent biceps jerk) are associated with spastic paraparesis.
- Lesions at C6–C7 result in spastic paraparesis along with weakness of wrists and hands (shoulder and elbow movements are spared). Lesions at C8–T1 cause a Horner syndrome along with spastic paraparesis and weakness of small muscles of the hands. A C7 lesion results in an absent triceps jerk.
- Lesions of the thoracic spinal cord result in spastic quadriparesis, sensory loss to a level, bowel-bladder incontinence and sexual dysfunction.
- Lesions at L1 result in spastic paraparesis, weak lower abdominal muscles and brisk patellar and ankle jerks. Lesions at L3 also manifest with spastic paraparesis but the abdominal muscles are spared and the patellar jerk is diminished but the ankle jerk is brisk.
- Lesions at S1–S2 results in weakness of the triceps surae, flexor digitorum longus, flexor hallucis longus and small muscles of foot. The ankle jerk is absent though the patellar jerk is preserved.
- Lesions at S3–S5 involve the *conus medullaris*; they present with bilateral signs, early loss of bowel and bladder control, *saddle anesthesia,* and an absent anal reflex. Conus lesions do not cause lower extremity weakness (unless roots are involved).
- Lesions of the *cauda equina* are most often unilateral at onset; they present with unilateral hyporeflexic paresis of the lower extremities affecting the feet and the toes, along with prominent radicular pain. Saddle anesthesia is a late feature and, typically, the sphincters are spared.

Spinal cord compression

- *Acute* spinal cord compression is usually the result of trauma and presents as a combination of segmental signs and long tract sensorimotor signs. *Subacute* spinal cord compression is usually due to an epidural or subudural abscess, hematoma, hemorrhage into a tumour or a herniated intervertebral disc.
- *Chronic* spinal cord compression may be due to bony or cartilaginous herniations into the spinal canal or due to slow-growing neoplasms. *Intramedullary* tumours are characterised by *funicular* pain (diffuse dull ache) and *dissociated* anesthesia with sacral sparing.
- Corticospinal tract signs are late. On the other hand, *extramedullary* tumours present with radicular pain and a *Brown-Sequard type* of syndrome (hemisection of cord); there is early involvement of corticospinal tracts and a loss of sacral sensation.

Non-compressive myelopathy

- The important causes of non-compressive myelopathy include transverse myelitis (postviral, multiple sclerosis), lathyrism, drugs (enteroquinol), vitamin B_{12} deficiency (subacute combined degeneration) and vascular abnormalities of the spinal cord.

Syringomyelia (syringobulbia)

- A syrinx is a fluid-filled cystic cavity in the central spinal cord (syringomyelia) or brainstem (syringobulbia).
- A syrinx may have a variable extent and often begins in the cervical spinal cord. It may be secondary to a tumour or may be associated with an Arnold-Chiari malformation.
- The clinical hallmark is *dissociated sensory loss* (pain and temperature loss without loss of touch or pressure sensations); there is often a cape-like sensory deficit over the shoulders and back, along with spasticity and weakness of the lower extremities (the latter due to corticospinal tract involvement). Wasting of small muscles of the hands and Charcot joints are additional features. Syringobulbia additionally results in involvement of the lower cranial nerves.
- An MRI is the investigation of choice, if available. Myelography followed by a delayed CT scan is an alternative imaging technique.
- The treatment includes surgical decompression of the syrinx along with treatment of the underlying cause (if any).

9.12 Infections of the central nervous system

ACUTE MENINGITIS

Meningitis is an inflammation of the arachnoid, pia mater and the intervening cerebrospinal fluid. Depending on the cause of the inflammation, meningitis may be aseptic or infective. Infective meningitis may be due to a virus, bacterium or fungus. Acute bacterial meningitis is discussed below.

Epidemiology The three organisms responsible for most cases of adult meningitis are Neisseria meningitidis, Hemophilus influenzae and Streptococcus pneumoniae. H. influenzae is more common in children and S. pneumoniae is the most common agent in the elderly. Other causes of meningitis usually seen in infants and the immunocompromised include Listeria monocytogenes, pseudomonas and other gram-negative bacteria, staphylococcus and group A streptococci. Hospital-acquired meningitis (such as postoperative meningitis) is usually due to gram-negative bacteria like E. coli, Klebsiella-enterobacter and Pseudomonas aeruginosa.

Pathology Since the subarachnoid space is continuous over the surface of the brain and the spinal cord, meningitis is not localised. However, purulent exudate tends to accumulate in the basal cisterns and the lateral sulcus. If the treatment is initiated rapidly, the inflammation resolves completely. A potential complication of fulminant meningitis is the development of edema of the brain which may result in uncal or tonsillar herniation. Other complications usually seen in inadequately treated meningitis are:

1. damage to the cranial nerves: the nerves most commonly affected are the eighth (auditory), third and sixth;
2. occlusion of cortical arteries as they pass through the exudates, resulting in cerebral infarction;
3. cortical thrombophlebitis;
4. hydrocephalus which may be obstructive (obstruction within the ventricular system) or communicating (extraventricular obstruction);
5. subdural effusions and empyema: subdural effusions occur most frequently in infants and manifest as an increase in head circumference; and
6. rarely, ventricular empyema.

Pathogenesis The common route of meningeal infection is through the upper respiratory tract. In pneumococcal and gram-negative infections, bacteremic spread is the probable path. Hence, infections of the gastrointestinal or urinary tract could precede acute bacterial meningitis. In fulminant meningitis, some of the local damage (as in nerve involvement) and systemic manifestations appear to be related to cytokinin release as part of the patient's immune response.

In rare cases, a patient may present with multiple attacks of meningitis. If these attacks are due to infective meningitis, CSF rhinorrhea should be checked for.

Clinical features Fever, headaches, neck stiffness and altered sensorium are the cardinal signs of acute meningitis. The altered sensorium may be in the form of confusion, delirium or coma. The fever is usually of a short duration (1–3 days). On examination of the nervous system, there are typically no focal neurologic signs. Neck stiffness is manifested as pain on flexion of the neck and as positive Kernig's or Brudzinski's signs (Fig 9.38). Elderly patients and those with underlying serious medical conditions may not manifest all these classical features; instead they may present with only lethargy and deterioration of sensorium. Seizures, generalised or focal, may occur in upto 20 per cent of patients. Papilledema is extremely rare.

Patients with meningococcal meningitis may show a petechial, purpuric or ecchymotic rash. This should be carefully looked for as it may be restricted to one or two tiny petechial spots. Patients with a florid rash usually have concomitant meningococcemia and are at high risk of hypotension, septic shock and disseminated intravascular coagulation.

As the patient is recovering from meningitis, non-neurologic complications which may prolong recovery include pneumonia, urinary tract infection (often provoked by urinary catheterisation), aortic valve endocarditis (pneumococcal), pyogenic arthritis, pericarditis, thrombophlebitis at the site of antibiotic administration and, in rare cases, drug fever (allergic response to penicillin, often but not invariably associated with eosinophilia).

Investigations When a patient presents in the emergency room with a clinical picture suggestive of bacterial meningitis, the priority is to obtain a reasonable confirmation of the diagnosis and initiate therapy as rapidly as possible and certainly *within thirty minutes.* Next, it is necessary to identify the causative organism so that the antimicrobial therapy can be more precise.

The patient's condition is made stable and intravenous access is established. An intradermal test dose of penicillin is administered. A rapid general physical and neurologic examination is done. If there is no papilledema or focal neurologic signs, blood is drawn for hemogram, biochemistry (particularly blood glucose) and blood cultures. A lumbar puncture (spinal tap) is performed next. In addition to estimation of glucose, protein and cell counts (cell counts should be done immediately), the CSF should be spun and Gram stain of the sediment should be examined.

Fig 9.38 Brudzinski's sign: passive flexion of neck causes spontaneous flexion of the lower limbs

If gram-positive organisms are seen pneumococcal meningitis is most likely. Gram-negative organisms suggest H. influenzae or Neisseria meningitidis. Bacterial antigens can be rapidly detected using counterimmunoelectrophoresis (CIEP), or latex agglutination tests which are inexpensive and easy.

The gross appearance of the CSF may range from clear to purulent. Typically, there are about 10,000 cells/mm^3, more than 80 per cent of which are polymorphonuclear leucocytes. If the patient has received inadequate antibiotic therapy (a common situation in India where a patient may have received antibiotics for a febrile illness prior to recognition of meningitis), cell counts may range from 1000 cells/mm^3, with upto 70 per cent being mononuclear cells. In this situation, differentiating between a partially treated meningitis and a subacute onset of a chronic meningitis (tubercular meningitis) may be difficult. The history is the most important clue and a chest X-ray may be helpful if active lesions of pulmonary tuberculosis are evident. If the clinical situation is unclear, simultaneous initiation of antibacterial and antitubercular therapy is a practical alternative. If the patient recovers within 7–10 days, bacterial meningitis is the more likely diagnosis and the antitubercular therapy is discontinued while keeping the patient under careful observation. If there is no recurrence of symptoms, antitubercular therapy need not be restarted. CSF glucose is reduced to less than 50 per cent of a simultaneously obtained blood glucose level and is often less than 40 mg/dl. CSF protein is elevated above 100 mg/dl and C-reactive protein is increased. Other diagnostic tests are serum electrolytes, renal function, and blood glucose (hypoglycemia may occur and should be corrected).

If the patient has papilledema or focal deficits, blood cultures are obtained and treatment started without attempting a spinal tap. A CT scan of the head is arranged as rapidly as possible. If the CT scan shows a mass lesion, alternative diagnoses such as a brain abscess should be considered. If there is no mass lesion, a lumbar puncture may be performed. Another utility of a contrast-enhanced CT scan of the head is in differentiating between bacterial and tubercular meningitis: enhancing exudates in the basal cisterns are more common in chronic meningitis such as tuberculosis. Finally, a CT scan may be of help in diagnosing the various complications described earlier but should only be done if there is clinical suspicion of such a complication (stroke, subdural empyema, or hydrocephalus).

Management Bacterial meningitis is a life-threatening emergency. Antimicrobial therapy should be started as soon as possible. If the Gram stain and clinical clues do not suggest a specific etiologic agent, empirical antibiotic therapy is initiated. The treatment of choice is penicillin G administered intravenously (2 million units every 2 hours). This is adequate for Neisseria meningitidis and used to be considered adequate for pneumococcal meningitis. The recent description of penicillin-resistant pneumococci, and the known lack of response in H. influenzae meningitis (to penicillin G) has made a combined regimen of penicillin in the above dose along with chloramphenicol (1 gram i.v. q 4 hours). Chloramphenicol has the advantage that it crosses the blood-brain barrier readily; on the other hand, it is a bacteriostatic rather than a bactericidal drug. Chloramphenicol-resistant H. influenzae are not common but have been reported. The treatment of choice for confirmed pneumococcal and meningococcal infection is intravenous penicillin in the doses described above; if resistance to penicillin is suspected, third-generation cephalosporins are the drugs of choice if available (cefotaxime [50 mg/kg i.v. q 6 hours, not to exceed 12 g/day] or ceftriaxone [75 mg/kg i.v. initial dose followed by 50 mg/kg i.v. q 12 hours, not exceeding 4 g/day]). For confirmed H. influenzae infection, a combination of ampicillin (2 g i.v. q 4 hours) along with chloramphenicol (in the above-

mentioned dose) is the regimen of choice. Third-generation cephalosporins are just as effective but more expensive.

The duration of antimicrobial therapy is usually ten days. Significant clinical recovery occurs in 24–48 hours. Within 72 hours, the patient may appear to be normal. Despite this, the full course of antibiotic therapy should be given. Repeat CSF examination is not indicated either during treatment or prior to discharge. There are, however, a few exceptions to this rule. If at the end of 48–72 hours, the patient has not shown a clinical response, a clinical reassessment takes place. As part of this assessment, along with an imaging study, a repeat lumbar puncture may be done. In pseudomonas meningitis, and in patients with meningitis following shunt insertion, periodic repeat CSF examinations are indicated to assess the therapeutic response. The duration of therapy in these patients is three weeks. If the response is inadequate, the foreign body (shunt) may have to be surgically removed.

Dexamethasone at a dose of 8 mg intramuscular every 12 hours for 3 days appears to reduce the risk of postmeningeal nerve deafness in children with H. influenzae meningitis. There is, however, an increased risk of gastrointestinal bleeding. In adults, the only proven role of dexamethasone is in patients showing signs of persistent cerebral edema; here, steroids are used along with intravenous mannitol.

All patients with meningitis should receive constant nursing to ensure prompt recognition of seizures and to prevent aspiration. If seizures do occur, phenytoin is administered acutely and continued for six months. If an underlying focus of infection such as mastoiditis is identified, it is usually treated surgically after recovery from meningitis but prior to discharge from the hospital.

Tuberculous meningitis, cerebral malaria and typhoid encephalopathy are important CNS infections which are described under the chapter ***Infections***. Tuberculous meningitis is by far the commonest cause of a subacute or chronic meningitic syndrome. The other two conditions present as fever, headache and altered sensorium with few, if any localising signs.

Chronic Meningitis

Causes of chronic meningitis include tuberculous meningitis, inadequately treated bacterial meningitis, fungal meningitis (most commonly cryptococcal), cysticercosis, meningeal carcinomatosis, syphilis and sarcoidosis. The clinical picture consists of headache with fever (most patients with infective meningitis) or without fever (carcinomatous meningitis, infective meningitis in immunosuppressed patients) and neck stiffness. Altered sensorium and papilledema may be seen but are not essential to make the diagnosis. Cranial nerve palsies may occur. Late complications, specially common in inadequately treated chronic meningitis, include obstructive or communicating hydrocephalus, seizures and arteritis (resulting in cerebral infarction). A CT scan with contrast administration demonstrates the presence of enhancing basal exudates. The diagnosis is established by CSF examination. The CSF protein levels are elevated (100–500 mg/dl) along with a mononuclear pleocytosis (100–500 white cells/mm^3, 90 per cent lymphocytes). In contrast, in acute meningitis 90 per cent of the cells are polymorphonuclear and the cell counts are in the thousands. CSF glucose levels may be low (10–40 mg/dl) but are not as low as in acute bacterial meningitis. The CSF should be examined for acid-fast bacilli, fungi and cytology. A chest X-ray should be taken and the fundus should be examined for tubercles. When a discernible pathogen is lacking, histologic and microbiolgic evaluations of bone marrow, liver or lymph nodes may be useful. Simultaneously a therapeutic trial of antituberculous therapy is initiated.

Cryptococcal Meningitis

Cryptococcal meningitis is due to infection of the meninges (and the subarachnoid space) with

Cryptococcus neoformans. The initial infection is in the lungs and is clinically silent. The rate of infection may be higher in patients exposed to droppings of pigeons and other birds. It is more frequently seen in immunosuppressed patients (such as those with HIV infection or those with diabetes mellitus). However, in more than 50 per cent of affected patients, there may be no evidence of immunosuppression.

Cryptococcal meningitis presents as a subacute or chronic basal meningitis. On pathological examination, there are clusters of cyst-like cavities filled with budding yeast forms. There is an infiltrate of lymphocytes, macrophages, and multinucleated giant cells. The clinical picture is usually more insidious than that of tubercular meningitis. Symptoms may initially include only headache, nausea, and vomiting. Later there may be fever, neck stiffness and papilledema. Cranial nerve palsies can result in blindness, diplopia, lower motor neuron-type of facial weakness and hearing impairment. Typically, there is bilateral involvement of multiple cranial nerves. Cognitive dysfunction is common and may later give way to altered sensorium and coma. Other complications include arteritis (resulting in cerebral infarction) hydrocephalus and seizures.

Untreated cryptococcal meningitis is almost uniformly fatal. With current therapeutic regimens, 75 per cent of patients survive; however, upto 50 per cent of the survivors may have serious neurologic sequelae. There is a 20 per cent relapse rate following cessation of therapy, even in patients who are not immunosuppressed. The relapse rate may be as high as 50 per cent for AIDS patients. These patients require life-long suppressive therapy. Most relapses occur in the first six months after treatment.

The diagnosis is made on examination of the CSF; India ink examination, which is rapid and effective, demonstrates the encapsulated yeast forms, being positive in 50 per cent (see chapter on infection). The CSF picture is like that of any other chronic meningitis. Fungal culture is not essential but serves to confirm the diagnosis. Immunological studies are also available to help demonstrate the presence of the cryptococcal antigen in CSF, and are positive in 80 per cent. A CT scan with contrast administration demonstrates the presence of enhancing basal exudates. Very rarely, there may be small non-enhancing cryptococcomas in the brain parenchyma.

The mainstay of therapy is the drug amphotericin B. Amphotericin B is an antifungal agent which acts by binding ergosterol in the fungal membrane. If given alone, the drug is started at a dosage of 0.2 mg/kg/day and then gradually increased to 1 mg/kg/day over a period of about the 1 week. More commonly, it is combined with flucytosine; this permits a lower dose of amphotericin to be used. In combination, the dose of amphotericin B is 0.3 mg/kg/day with flucytosine 150 mg/kg/day. These two antifungal drugs are discussed in the 'antibiotics' section. The total duration of therapy is 6 weeks or more. Amphotericin B is poorly absorbed from the gut; hence, it is given intravenously, dissolved in 5 per cent dextrose, as a slow infusion over 4–6 hours. Administration of aspirin, prochlorperazine and hydrocortisone (25–50 mg) before the infusion helps prevent fever, chills, nausea and hypotension during the infusion. Addition of 25 units of heparin to the infusion reduces the incidence of thrombophlebitis. The dose limiting side effect of amphotericin B is nephrotoxicity. Hypokalemia, anemia and thrombocytopenia can occur. Addition of flucytosine reduced the nephrotoxicity of amphotericin B but increases its hematological toxicity. Hence, in patients with AIDS on zidovudine, amphotericin may be used alone. A combined therapy is given for 6 weeks and then amphotericin alone may be continued for a further four weeks. Monitoring of therapy includes estimation of renal function, serum electrolytes and liver function tests thrice a week and periodic CSF examinations.

Patients with AIDS who have cryptococcal meningitis require lifelong maintenance therapy. Fluconazole (200 mg oral daily) is used for this purpose.

ACUTE VIRAL INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

Acute viral infections of the central nervous system may involve the meninges (in viral or aseptic meningitis), brain parenchyma (in viral encephalitis) or spinal cord (in myelitis). Two of these sites may be affected at the same time resulting in meningoencephalitis or encephalomyelitis. Often the responsible virus cannot be identified. The culprit virus usually enters the body through the respiratory tract (as in mumps) or through the gastrointestinal tract (poliomyelitis) and the nervous system is secondarily affected.

Aseptic Meningitis

This is a mild inflammation of the meninges with bacteriologically sterile cultures of the CSF (hence the term aseptic). Most cases of aseptic meningitis are caused by viruses. The clinical presentation is as a flu-like illness with headache, malaise, fever, and sometimes, photophobia. On examination there is mild neck stiffness but there are no focal neurological signs. The illness is self-limited. It develops over 24–48 hours and resolves in 3–10 days. The concern at the time of clinical presentation is to rule out acute bacterial meningitis. This is easily accomplished by examination of the CSF. The CSF has a normal protein and glucose content. There is a mild mononuclear pleocytosis (cells: 10–100/mm^3, 75% lymphocytes). This CSF picture may be seen in *connective tissue disorders* such as, systemic lupus erythematosus and in other *immunoinflammatory diseases*, like sarcoidosis, Behcet syndrome, Vogt-Koyanagi-Harada syndrome,[1] which are also classified as types of aseptic meningitis. A *chemical* meningitis following the introduction of drug or contrast into the thecal space can also cause an aseptic meningitis. The CSF picture needs to be distinguished from the similar picture seen with *parameningeal* infections. The latter commonly results in an elevation of CSF protein content. If there is a doubt, a contrast-enhanced CT scan of the head serves to provide the distinction between the two conditions. The CSF picture in *chronic meningitis* may resemble that of aseptic meningitis but CSF glucose levels are diminished in chronic meningitis while they are normal in aseptic meningitis. Other diagnostic tests in aseptic meningitis include serological studies for the suspected virus, viral cultures of the stools, urine and throat swab, and peripheral white blood cell counts, which are normal in two-thirds of the patients and show leukopenia in the rest.

[1] A rare disorder characterised by uveitis, depigmentation, deafness and meningitis (uveomeningeal fever)

Viral Encephalitis

The term encephalitis implies a clinical and pathological involvement of the brain parenchyma. This may involve cerebral hemispheres, the brainstem (brainstem encephalitis) or both.

Etiology The various causes of viral encephalitis are listed below. Some types such as rabies and herpes simplex encephalitis cause distinctive clinical syndromes. Others such as Japanese-B encephalitis do not. Encephalitis due to herpes simplex is discussed below. It is important because it is the one form of encephalitis with effective drug therapy. Others are discussed under **Infections**.

Viruses causing encephalitis

- Herpes simplex
- Rabies
- Cytomegalovirus
- Arboviruses (for example, Japanese B, Kyasanur forest disease)
- Enteroviruses
- Influenza
- Mumps, measles
- Arena viruses (lymphocytic choriomeningitis)
- Adenovirus 70
- Others

Pathology There are widespread lesions involving the grey matter of the cerebral cortex, diencephalon, upper brainstem and, less commonly, the cerebellar cortex. There is neuronal death, appearance of microglial nodules and lymphocytic infiltration around the blood vessels as well as the meninges. In severe cases (particularly with Japanese B encephalitis), there may be focal neutrophilic infiltration, vasculitis and petechial hemorrhages.

Clinical features Clinically, the patient presents with an initial upper respiratory, gastrointestinal illness or a flu-like prodrome followed in 2–3 days by headache, fever, neck stiffness and altered sensorium. Seizures may occur and focal neurologic deficits may be seen. Systemic features may help one to suspect a specific virus; for example, rash may be seen with Coxsackie and echovirus infection, or parotitis with mumps. Focal encephalitis involving chiefly the brainstem structures, may occur and is known as *brainstem encephalitis.*

Herpes simplex encephalitis

Herpes simplex encephalitis is the single commonest cause of acute encephalitis, accounting for 10–30 per cent of all encephalitides. It is also the *only treatable acute viral encephalitis.* In adults the causative organism is usually the Type I virus (HSV-I). In neonates, infection is due to HSV II contracted during vaginal delivery if the mother has genital herpes.

Pathology and pathophysiology HSE is secondary to reactivation; the initial infection is oral and the virus spreads by retrograde axonal transport to the trigeminal ganglion where it remains in a dormant state. For an unknown reason, the virus becomes reactivated and is carried by the leptomeningeal fibres to portions of the brain close to the trigeminal ganglion, that is, the temporal pole and the orbitofrontal region.

Pathology The involved areas show hemorrhagic necrotising lesions. The typical distribution of these lesions is the mesial temporal lobe and basal frontal region. Lesions are commonly bilateral. A microscopic examination shows necrosed vessels with intravascular thromboses and inflammatory infiltrates (mostly lymphocytes with a few polymorphonuclear cells). Neurons and glial cells show necrosis and intranuclear eosinophilic inclusion bodies (Cowdry type A).

Clinical features Herpes simplex encephalitis presents with a typical picture of any acute encephalitis: there is fever, headache, altered sensorium and, sometimes, seizures. Signs suggesting herpes simplex virus as the etiology of an encephalitis are those indicating a focal lesion in the inferomedial temporal and frontal lobes. These signs may be clinical, such as, behavioural abnormalities, motor aphasia, hemiparesis, olfactory or gustatory hallucinations, complex partial seizures or focal motor seizures (as opposed to generalised tonic-clonic seizures that may be seen with any type of encephalitis). EEG or radiologic signs pointing to temporal lobe involvement also strongly suggest herpes simplex encephalitis.

Typically, the patient has a non-specific 'viral' prodrome followed either by bizarre behaviour or drowsiness with speech difficulty. The mental status deteriorates over 7–10 days until the patient becomes comatose. Diagnosis should be made within the first 24–48 hours of presentation. In fulminant cases there may be uncal herniation and death within 48–72 hours.

Investigations The cerebrospinal fluid is suggestive of an acute encephalitis showing mononuclear pleocytosis (10–500 cells/mm^3, usually <200 cells/mm^3). There is a mild increase in proteins and a decrease in CSF glucose. Unlike other encephalitides, however, herpes simplex encephalitis usually shows a large number of red blood cells (approximately 1000/mm^3) and there may be occasional xanthochromia.

Imaging studies may be normal in the initial stages and repeat scanning in 24–48 hours may be required. The contrast-enhanced CT is positive in 50–60 per cent of subjects (Fig 9.39). There is hypodensity of the temporal poles surrounded by an irregular ring of enhancement and an outermost zone of edema (*meniscus sign*). The MRI studies show a T1 hypointense, gadolinium non-enhancing area with surrounding edema (T2 hyperintense) and scattered areas of hemorrhage within the lesion.

The EEG initially shows diffuse, generalised slowing with later periodic, high-voltage, temporal sharp and slow wave complexes. Brain biopsy is rarely done nowadays although it is the only definitive means of establishing the diagnosis. The reason brain biopsy is avoided include the real, although small, danger involved in the procedure, the time lost in waiting for the procedure and its results and the fact that current generation therapy is fairly safe. With a blind needle biopsy, there is high risk of hemorrhage and with an open biopsy there is the risk involved in operating on an acutely sick patient. If a biopsy is done, rapid detection of the virus using fluorescent antibodies is undertaken.

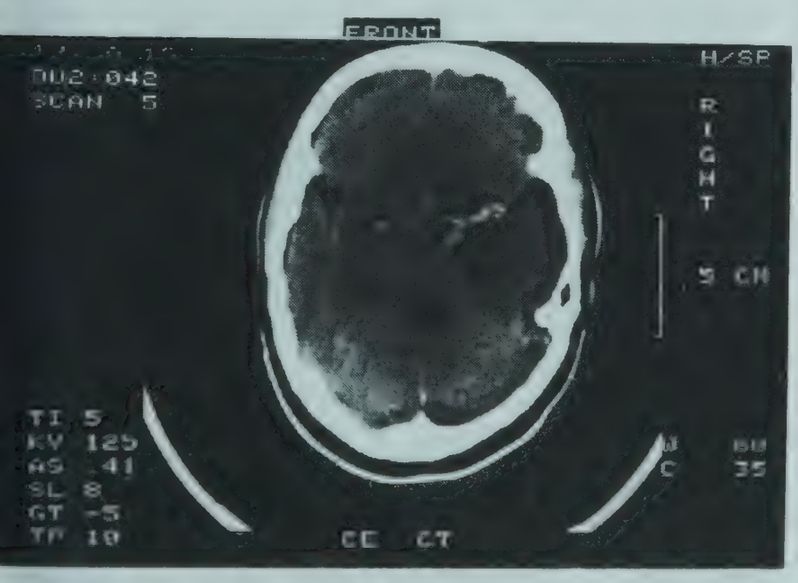


Fig 9.39 The scan shows right temporal pole hypodensity in a patient with herpes simplex encephalitis. This young girl recovered on acyclovir therapy.

Detection of viral antigen in the cerebrospinal fluid by the polymerase chain reaction is a fairly sensitive and specific confirmatory test. Rising IgM antibody titres are confirmatory but are of little clinical utility.

Treatment Acyclovir (Zovirax) is the treatment of choice; it is given intravenously at a dose of 30 mg/kg. Acyclovir is a selective inhibitor of viral DNA polymerase. Since the drug has to be activated by an intraviral enzyme thymidine kinase, acyclovir is not toxic to the patient's cells. The principal side effect is transient renal insufficiency and can be avoided by keeping the patient well hydrated. Unfortunately, the drug is expensive and may be hard to obtain in India. The alternative is intravenous vidarabine (15 mg/kg/day) as a slow infusion over twelve hours. Oral acyclovir is readily obtained but its efficacy in encephalitic herpetic illness may be limited.

Prognosis Without treatment, 30–70 per cent of herpes simplex encephalitis patients die; the the rest are left with serious sequelae. Less than 1 per cent of patients return to a normal functional state. If acyclovir treatment is initiated while the patient is still conscious (within the first four days), over 90 per cent survive and 40 per cent return to near normalcy. The sequelae of herpes simplex encephalitis include global dementia, dysphasia, seizures and memory impairment (Korsakoff-type amnesia).

Viral Myelitis

Viral myelitis may be caused by polio virus, Coxsackie and echoviruses (enteroviruses). All these viruses result in a similar clinical picture of asymmetrical lower motor neuron type of paralysis. Poliomyelitis is the most common example of this picture. Herpes simplex can spread from the genital region to the sacral spinal cord and the most prominent clinical feature is involvement of the bowel and bladder (conus syndrome). Herpes zoster may also cause

a myelitis. Myelitis due to the retrovirus HTLV-1 is discussed under demyelinating disorders.

The **slow virus** infections present as dementia and include subacute sclerosing panencephalitis (SSPE), Creutzfeldt-Jakob disease (CJD), kuru, progressive multifocal leukoencephalopathy (PML) and the AIDS-dementia complex. These are discussed in the chapter **Infections**.

PARAMENINGEAL INFECTIONS

The term parameningeal infection is used for a group of localised pyogenic infections occurring in structures close to the meninges but not directly invading the pia-arachnoid. This group of infections includes infections of the brain parenchyma (brain abscess), epidural space (spinal epidural abscess), subdural space (subdural empyema) and dural sinuses (septic thrombophlebitis). All parameningeal infections result in an aseptic inflammatory response in the pia-arachnoid. This is reflected in the CSF as a mild lymphocytic pleocytosis of less than 100 cells/mm^3, mild elevation of protein (50–100 mg/dl) and a normal CSF glucose.

Brain Abscess

Etiopathogenesis Brain abscesses are bacterial in origin. The causative organisms include aerobes (such as Streptococci and Staphylococci) as well as anerobes (notably Bacteroides). More than one bacterium is cultured from 50 per cent of brain abscesses.

The infection spreads to the brain parenchyma from the middle ear or mastoid (in 25%), paranasal sinuses, following head trauma or craniotomy (in 25%) and by hematogenous spread (in 50%). In cases attributable to blood-borne infection, the most common primary focus is chronic lung disease. Other sources are skin, bone and pelvic infections. In patients with cyanotic heart disease (such as tetralogy of Fallot), the risk of a brain abscess is increased.[1] In brain abscess due to contiguous spread there is usually a single focus, whereas in blood-borne infections multiple abscesses are seen. Bacterial endocarditis rarely causes a brain abscess. Bacteroides are cultured from otogenic (that is, related to ear disease) brain abscesses, staphylococci from posttraumatic abscesses and streptococci in patients with cyanotic heart disease.

Pathology Ear infections spread to the inferior temporal lobe or the ipsilateral cerebellar hemisphere. Infection from the paranasal sinuses spreads to the frontal lobes.

Hematogenous brain abscesses are located in the distribution of the middle cerebral artery. A brain abscess begins as a localised focus of inflammation and edema– the stage of cerebritis. Local vessels become thrombosed and the area undergoes liquefaction necrosis. Finally, fibroblasts form a capsule around the central area of accumulated pus– this is the stage of encapsulation. Each stage develops over approximately one week.

Clinical features The patient presents with symptoms suggestive of raised intracranial tension such as headache, vomiting, drowsiness, and may have seizures. Focal signs may or may not be present depending on the size and location of the abscess; for example, a prefrontal abscess may present with only hypobulia or perhaps a positive grasp reflex on the opposite side. Fever is present in 50 per cent, neck stiffness and papilledema in 25 per cent and hemiplegia in 10 per cent.

Investigations The diagnosis is suspected based on the history and may be confirmed with a contrast-enhanced CT scan. During the stage of cerebritis a hypodense area with irregular

[1] Septic emboli from the venous system can enter the arteries through the right to left shunt. Hypoxemia also renders brain tissue more vulnerable.

enhancement is seen. An encapsulated abscess is seen as a central non-enhancing hypodensity, surrounded by an area of ring enhancement, outside which is a large non-enhancing area of brain edema. Other causes of ring enhancement are brain tumours, tuberculoma, and resolving cerebral infarction: all these conditions should be considered in the differential diagnosis.

Treatment If the diagnosis is made during the stage of cerebritis, antimicrobial therapy may be sufficient to effect a cure. The preferred antibiotics are a combination of Penicillin G (2 million units i.v. q 2 hours) and metronidazole (1 i.v. q 6 hours). Cefotaxime or chloramphenicol may be added in the same doses as used for meningitis. If staphylococcal infection is suspected, cloxacillin (1–1.5 q 6 hours) is used instead of Penicillin G. The duration of treatment is 6–8 weeks and the response is assessed clinically and by repeat imaging. For a well-defined brain abscess, surgical excision is followed by the same course of antimicrobial therapy. If the abscess is deep, it is aspirated and this aspiration may be CT-guided. If there are multiple abscesses, medical therapy is preferable to surgery. If pus is obtained either by aspiration or at surgery, Gram stain, aerobic and anerobic cultures should be performed on the specimen and subsequent antimicrobial therapy guided by the results. Mortality is only 10–15 per cent with adequate treatment. An occasional complication is focal epilepsy which may require anti-convulsant therapy.

Subdural Empyema

Subdural empyema refers to a localised suppuration in the space between the dura and the arachnoid mater. It originates by the spread of infection from contiguous sites which may be the paranasal sinuses, mastoid, osteomyelitis of the skull bones or a brain abscess. The bacteria are polymicrobial as in a brain abscess. Pathologically, there is a variable amount of pus (5–200 ml), some pial infiltration and thromboses of cortical veins. Inflammation of the dura, the arachnoid and thromboses of dural venous sinuses in the vicinity may be seen. The underlying brain may be compressed. There is headache, fever, vomiting and altered sensorium. Seizures, mild neck stiffness and focal neurologic signs, such as, hemiparesis may be present. Papilledema occurs in about 50 per cent. The major differential diagnosis is from a brain abscess. A CT scan of the head shows an elliptical density in the subdural space, the arachnoid margin of which is strongly enhancing. Examination of the CSF shows an elevated protein content (75–300 mg/dl), mild pleocytosis (5–500 cells/mm^3, both neutrophils and lymphocytes) but a normal glucose content and absence of any bacteria on smear and culture. Treatment consists of surgical drainage and the same antibiotic regimen as described for treating brain abscesses. Mortality is reduced from 100 per cent in the untreated patient to only 10 per cent in the adequately treated patient.

Cranial Extradural Abscess

This is usually secondary to osteomyelitis of the adjacent skull bone. The osteomyelitis itself may be a consequence of infection within the paranasal sinuses or the mastoid. The patient may present with only headache and no focal neurological signs. The CSF is normal on examination and the diagnosis is made on the basis of a CT scan of the head. Treatment consists of surgical drainage and antibiotics.

Spinal epidural abscess is discussed in the section on the spinal cord.

Septic Intracranial Thrombophlebitis (Infection of the Dural Venous Sinuses)

Lateral sinus thrombophlebitis usually follows otitis media or mastoiditis. There is pain and discharge from the affected ear followed a few days later, by fever and symptoms of raised intracranial tension. Later, there may be drowsiness and seizures. On examination, there is swelling, tenderness and distended veins over

the ipsilateral mastoid process. Neck movements may be painful. Ipsilateral or bilateral papilledema may be seen. Focal neurologic signs are uncommon. If the infection spreads to the inferior petrosal sinus, there may be involvement of the ipsilateral trigeminal and abducens nerve. There may be a preexisting hearing impairment on the affected side.

Cavernous sinus thrombosis results from an infection in the 'dangerous area of the face' or less commonly from a pharyngeal infection spreading via the petrosal sinuses. The clinical picture begins with fever and headache and the first localising symptoms may be pain in one eye, periorbital edema, ptosis or diplopia. There is impairment of venous drainage from the orbit into the cavernous sinus causing conjunctival redness, chemosis, periorbital edema and proptosis. There is involvement of the nerves that pass through the cavernous sinus: the third, fourth, ophthalmic and maxillary branches of the fifth, and the sixth cranial nerves (Fig 9.40). The third nerve involvement affects the pupils as well as the eyelids and the extraocular muscles. Examination of the fundus may show retinal hemorrhages and papilledema. The symptoms usually start on one side but rapidly spread to the other side since there are numerous connections between the two cavernous sinuses. Vision may be lost early or may remain relatively spared and sensorium may remain intact until late in the illness. The differential diagnosis is given in Table 9.36.

Examination of the CSF reveals a parameningeal picture as seen with a brain abscess. A contrast-enhanced CT scan of the head may be normal or may show enlargement of the affected sinus. An MRI shows the absence of bloodflow within the sinus.

Superior sagittal sinus thrombophlebitis occurs following a compound fracture of the skull, meningitis, sinusitis of the ethmoidal or maxillary sinuses or, in rare cases, following a neurosurgical procedure. There is secondary aseptic thromboses of the adjacent cortical veins resulting in headache, drowsiness, seizures and hemiparesis. Contrast-enhanced CT scan and MRI show absence of bloodflow within the sinus.

Treatment of dural sinus thrombophlebitis consists of surgical drainage of the original focus of infection (in the bone, mastoid, etc.) and broad spectrum antibiotics. The causative organisms are usually Staphylococcus aureus, anerobic streptococci, and sometimes, gram-negative bacteria. Hence, treatment consists of a penicillinase-resistant penicillin (cloxacillin 1–2 g i.v. 6 hourly), metronidazole (1 g 6 hourly) and gentamicin (80 mg i.v. 2–3 times a day).

Aspergillosis

Aspergillosis can present as isolated fungal infection of the CNS or with concomitant involvement of the lung and other organs. It occurs in patients with a hematological malignancy, those using broad spectrum antibiotics and corticosteroids or following a craniotomy. The lesions may be frontotemporal (extension from paranasal sinuses) or as multiple microabscesses at the junction of cerebral

Table 9.36 Differential diagnosis of cavernous sinus thromboses

Etiology	*Distinguishing features*
Orbital cellulitis	unilateral, preceding ocular infection, maxillary V spared
Mucormycosis	seen in diabetics (details in text)
Tolosa-Hunt syndrome	unilateral, patient not acutely ill
Carotico-cavernous fistula	ocular bruit, afebrile
Sphenoid wing meningioma	gradual onset, often unilateral

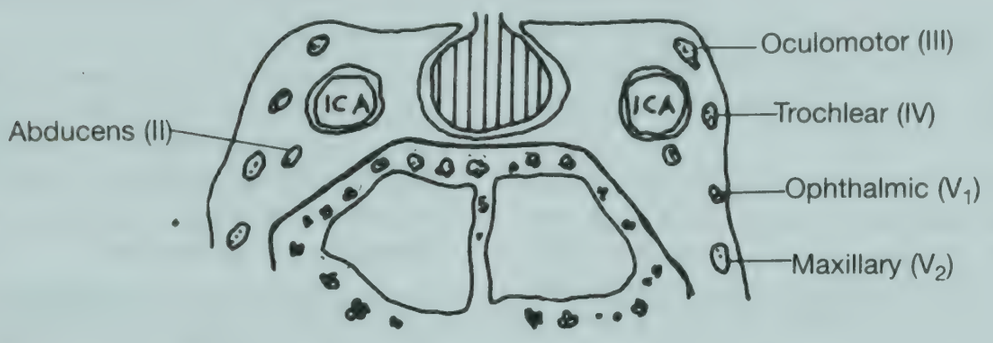


Fig 9.40 Cavernous sinus (coronal section)

cortical grey and white matter. The fungus has a propensity to invade blood vessels causing thrombosis and hemorrhage. The clinical presentation is with headache, fever and altered sensorium. Stroke, seizures, proptosis, papilledema and multiple cranial nerve palsies may occur. The CSF shows a 'parameningeal infection' picture but also shows red blood cells. The CT scan shows ring enhancing lesions. the biopsy shows septate hyphae branching at acute angles. Treatment consists of amphotericin B (1 mg/kg/day). Rifampicin or flucytosine may be added.

Mucormycosis

This is a serious fungal infection presenting clinically with a picture similar to cavernous sinus thrombosis but in the setting of diabetic ketoacidosis (characteristic) or other causes of immunosuppression. The acidosis appears to favour the growth of mucor; so patients with chronic renal failure or other causes of metabolic acidosis are also susceptible. If there is an associated nasal or palatal ulcer, a potassium hydroxide mount of a swab specimen shows broad, non-septate hyphae branching at right angles. The CSF shows a 'parameningeal infection' picture. CT and MRI show changes in the cavernous sinus, opacification of the paranasal sinuses and erosion of adjacent bone. The treatment is to correct the underlying metabolic abnormality and start treatment with amphotericin B despite which over 40 per cent of patients die.

Neurological complications of infective endocarditis

In subacute bacterial endocarditis, there may be diffuse encephalopathy due to focal embolic encephalitis with many tiny emboli occluding vessels, an embolic infarct, or in 5 per cent of patients, a mycotic aneurysm. Brain abscesses are rare unless the endocarditis is acute (e.g. staphylococcal endocarditis). The mycotic aneurysms are more distal than berry aneurysms and may resolve with antibiotics. Rupture remains a possibility and sometimes surgery is performed after the course of antibiotics is over. Routine screening for an aneurysm is not required in all patients.

KEY CONCEPTS

Meningitis

- ➢ This refers to acute or chronic infection and inflammation of the meninges.
- ➢ Acute meningitis is most often bacterial in origin; Hemophilus influenzae, pneumococcus and meningococcus account for most cases of bacterial meningitis. Viral meningitis (aseptic meningitis) is most often due to enteroviruses.
- ➢ Clinical features include the onset of high grade fever, headache, neck pain with positive Kernig's or Brudzinski's signs. Petechial rash suggests meningococcal meningitis.

- *Chronic meningitis* is due to infection with tuberculosis, cryptococcus (and other fungi). Often chronic meningitis occurs as a basilar meningitis with multiple cranial nerve palsies.
- CSF examination is the investigation of choice. Acute bacterial meningitis results in a purulent appearance with increased polymorphonuclear cells, increased proteins and decreased glucose level. The CSF must be examined with Gram's stain and subjected to culture; latex agglutination tests help detect specific bacterial antigens rapidly. Viral meningitis is associated with increased mononuclear cells, increased proteins but normal glucose levels (mumps and HSV are exceptions). In chronic meningitis, there is an increase of mononuclear cells in the CSF, with moderately elevated proteins and reduced glucose levels. A Ziehl-Nielsen stained preparation and an India ink preparation must be obtained in every case of chronic meningitis.
- The treatment of meningitis is with appropriate antimicrobials to which the infecting organism is sensitive.

Cryptococcosis

- This is an infection by a yeast (*Cryptococcus neoformans*). Immunosuppressed individuals are at higher risk.
- Presentation is as a subacute lobar pneumonia or as a chronic basilar meningitis (headache, meningismus, low grade fever, lower cranial nerve palsies).
- The diagnosis of cryptococcal meningitis is by CSF examination (lymphocytic meningitis); the organism may be demonstrated with an *India ink* preparation; the antigen may be detected with a latex agglutination test.
- Meningitis requires two drugs: fluconazole or amphotericin B along with flucytosine; indefinite treatment may be required in AIDS patients.

Brain abscess

- A brain abscess is an intracerebral encapsulated collection of pus. Brain abscesses may arise due to direct extension (mastoiditis, sinusitis, otitis media, head injury), or bacteremia (endocarditis, congenital cyanotic heart disease, i.v., drug abuse). A majority of abscesses are polymicrobial.
- The initial stage of cerebritis is followed by parenchymal necrosis and 'walling off' by reactive gliosis and fibroblasts.
- Clinical presentation is with fever, headache, nausea, vomiting and signs of raised intracranial tension and focal neurologic deficit.
- A contrast-enhanced CT scan is the investigation of the choice; the abscess appears as a hypodense lesion with an enhancing rim. Avoid lumbar puncture due to the risk of herniation.
- Treatment with antibiotics must continue for 6–8 weeks. Early aspiration is recommended once the abscess is encapsulated. Corticosteroids or osmotic diuretics are adjuncts for lowering raised intracranial tension.

Septic thrombophlebitis of dural sinuses

- The infection of intracranial dural sinuses usually arises by contiguous spread from a focus (sinusitis, otitis or mastoiditis).
- *Cavernous sinus* involvement results in exopthalmos, diplopia, variable paresis of cranial nerves III, IV and VI, ptosis, photophobia and papilledema. *Superior sagittal sinus* infection results in leg weakness, abnormal mental status, papilledema and seizures. *Lateral sinus* infection manifests with facial pain, edema over the ear and VI nerve palsy (*Gradenigo's triad*).
- Diagnosis is clinical and MRI is the investigation of choice.
- The treatment consists of the administration of appropriate doses of intravenous antibiotics.

9.13 Demyelinating diseases of the central nervous system

MULTIPLE SCLEROSIS

Multiple sclerosis is a disease of young adults characterised by a chronic vulnerability of the white matter within the central nervous system (optic nerve, spinal cord and brain) to recurrent episodes of inflammation and demyelination resulting in clinical symptoms.

Epidemiology Multiple sclerosis is a disease of young adults typically affecting individuals between the ages of 10 and 50 years although the disease is not unknown at other ages. The disease shows a number of interesting predilections:

1. Women are affected more often than men (ratio 3:2).
2. Caucasians have a higher incidence than Negroids.
3. Areas of the world with a temperate climate report a higher incidence than the tropics.

These clues have not yet been synthesised into a coherent theory on the pathophysiology of multiple sclerosis. The only prevalence data available from India is for the Parsi community in Bombay: in this group the prevalence rate is 21 per 10,000.

Pathology The hallmark of multiple sclerosis is the white-matter plaque, a clearly defined patch of demyelination within the CNS. These lesions may be found throughout the CNS but certain sites appear to be especially vulnerable. These are the optic nerve, the brainstem, the spinal cord and the periventricular regions including the corpus callosum. Remyelination may occur in the demyelinated areas resulting in abnormally thin myelin sheaths within this area of the 'shadow plaque'.

Acute lesions are characterised by perivascular cuffing (venules surrounded by aggregates of T cells which have freshly entered the CNS), inflammatory cell infiltration (T and B lymphocytes and macrophages filled with myelin debris), oligodendrocyte loss and break-down of associated myelin sheaths and astrocyte proliferation. Chronic lesions show little inflammatory activity; the demyelinated axons are separated by a dense network of astrocytic processes and oligodendrocytes are absent.

Clinical manifestations The typical clinical picture of multiple sclerosis consists of a young adult who presents with an acute-onset neurological illness affecting the optic nerve (loss of vision), cerebellum (dysarthria, ataxia), brainstem (diplopia) or spinal cord (paraparesis, paresthesia, incontinence). The patient recovers significantly from the attack spontaneously over a few weeks and then after a few months has a second attack affecting another one of the regions enumerated above. Each period of neurological dysfunction is called a *relapse* and the periods of improvement are called *remissions.*

The clinical criteria for the diagnosis of multiple sclerosis were defined by Schumacher. In a simplified form, these criteria are: 1) age of

patient between 10 and 50 years; 2) predominantly white matter involvement; 3) at least two episodes lasting more than 24 hours each; 4) clinical evidence of involvement of two anatomically discrete sites within the central nervous system, and 5) no better alternative explanation for the clinical picture.

The clinical course of multiple sclerosis is variable; it may follow a *relapsing-remitting pattern* throughout the patient's life, or it may be initially relapsing-remitting and after 5–10 years result in steady deterioration of neurological status (a *chronic-progressive* course). A significant minority, particularly older patients, may show a chronic progressive course from the onset of the disease itself. In such patients, the disease should be present for at least six months in order to make the diagnosis.

A variety of clinical manifestations may be seen in patients. The clinical picture varies considerably between patients. Fatigue is common and is not explained purely by neurologic deficits. Subtle difficulties with abstract thought and recent memory may be seen but dementia is rare. If dementia does occur, it is seen late in the course of the disease. Personality changes in the form of depression or inappropriate indifference may be seen in 20 per cent of patients. All these changes in cognition and behaviour correlate with the extent of frontal lobe demyelination. Seizures are rare (3 per cent).

The most common cranial nerve involved is the *optic nerve.* The patient presents with blurring of vision, which worsens over 24 to 48 hours to partial or complete loss of vision in one eye. There may be pain in that eye, particularly with extraocular movements. An examination of the fundus may show swelling and hyperemia of the optic disc and a diagnosis of *optic neuritis* is made. If the optic nerve is involved at some distance behind the optic disc, there may be no visible abnormality of the disc, although the patient's symptoms are similar; this is called *retrobulbar neuritis.* There is gradual improvement of vision. A mild decrease in visual acuity or pallor of the disc may remain as sequelae. Often both optic nerves are involved at different times. Each optic nerve may be affected more than once. Cranial nerve involvement can also manifest as diplopia and nystagmus. *Internuclear ophthalmoplegia,* particularly if bilateral, is suggestive but not diagnostic of multiple sclerosis. *Trigeminal neuralgia* or *hemifacial spasms* may be seen.

Spinal cord lesions may affect the thoracic or cervical segments. There may be more than one site of involvement. In the early stages, paresthesia (tingling or numbness in one limb) is common. *Lhermitte's sign* is an electric shock-like sensation occurring on neck flexion and radiating down the spine into the legs. A transverse sensory level may be seen. Motor manifestations (spasticity and weakness) commonly affect both lower limbs (paraparesis) but monoparetic, hemiparetic and quadriparetic distribution of weakness may be seen. An upper motor neuron type of bladder dysfunction, constipation and sexual dysfunction are common.

Cerebellar involvement commonly presents as gait ataxia, while limb ataxia, dysarthria, titubation and nystagmus can also occur.

A feature suggestive of multiple sclerosis is the transient worsening of preexisting symptoms when the patient is exposed to an increased temperature (fever, hot bath). This is called *Uhthoff's phenomenon.*

What causes a relapse of the disease is not clear. Stress, viral infections, vaccinations and pregnancy may all play a role. Most relapses do not have an identifiable cause.

The onset of the disease at a later age and a chronic progressive course are associated with a poorer prognosis. About 50 per cent of patients continue to walk even ten years after disease onset. Life expectancy is reduced by 25 to 50 per cent.

Investigations The laboratory investigations which can help support a clinical diagnosis o

multiple sclerosis are evoked potential studies, neuroimaging (CT/MRI) and examination of the CSF. Visual evoked responses are abnormal in 70–85 per cent of patients. They may be abnormal in patients who have completely recovered from an attack of optic neuritis (thereby providing objective evidence of a lesion). The somatosensory evoked responses are abnormal in about 60 per cent and brainstem auditory evoked responses in 40 per cent of patients (Fig 9.41a). The CT scan permits the exclusion of alternative diagnoses such as an infarct or a brain tumour. In a patient with multiple sclerosis, findings on the CT scan include periventricular white matter hypodensities. Some of these lesions are contrast-enhancing. The administration of a double dose of contrast followed by delayed scanning increases the percentage of contrast-enhancing lesions detected. Contrast-enhancement is thought to suggest *active* demyelination. MRI is the imaging technique of choice (Fig 9.41b), being positive in nearly all patients with multiple sclerosis. The plaque density on the MRI correlates well with disease progression. Plaque enhancement following infusion of gadolinium contrast suggests a new active lesion. Other diseases (systemic lupus erythematosus, vasculitis, sarcoidosis, Behcet syndrome, white matter infarcts, leukodystrophies) can result in an MRI appearance resembling that seen in multiple sclerosis. The involvement of the corpus callosum favours the diagnosis of multiple sclerosis.

In multiple sclerosis the CSF shows a normal total protein content and cell count in most patients. Concentrations of CSF immunoglobulins (IgG) are increased secondary to intrathecal synthesis. This may be measured as the IgG index[1] or seen as *oligoclonal bands* on CSF electrophoresis. When normal CSF is electrophoresed, the cathodal region shows a broad homogeneous 'blur' of polyclonal immunoglobulin. In multiple sclerosis, a few clones of plasma cells each produce large amounts of a single antibody. Each antibody presents as a dense band in the electrophoretic pattern. CSF oligoclonal bands are present in 95 per cent of patients.

[1] IgG index = $\frac{\text{CSF IgG} \div \text{Serum IgG}}{\text{CSF albumin} \div \text{Serum albumin}}$

The index is normally less than 0.66.

Pathogenesis Multiple sclerosis belongs to the category of autoimmune disorders. The details, however, are still being investigated. There appears to be an increased presentation of so-called 'MS' antigens by the macrophages and astrocytes within the central nervous system. There is also an increased entry of T lymphocytes into the central nervous system. The precipitating factor for both may be an as yet unidentified viral infection. The role of a genetic component in the pathogenesis of multiple sclerosis is suggested by the finding of concordance of the disease in 25 per cent of monozygotic twins (compared to 3 per cent of dizygotic twins). Contenders for the role of 'MS' antigen are myelin basic protein and myelin oligodendrocyte glycoprotein. The pathogenetic mechanisms are briefly displayed in Fig 9.42. The immunological terms used (such as T_H cell are discussed in **Immune Diseases**.

Treatment Treatment of multiple sclerosis involves providing symptomatic relief, attempts to hasten and improve recovery from an acute attack and attempts to alter the course of the disease.

Management of symptoms: A variety of neurologic impairments are seen in multiple sclerosis. The management of spasticity and sensory impairment is similar to that discussed under spinal cord lesions. Fatigue may be handled by teaching the patient to pace himself with 15 to 20 minutes of rest every two hours. Amantadine (100 mg bid) is beneficial in some patients. The effect of a cerebellar tremor on voluntary movements is diminished by using weighted utensils. Diplopia can be treated using a patch over one eye or with 'prism' glasses. Neuralgic

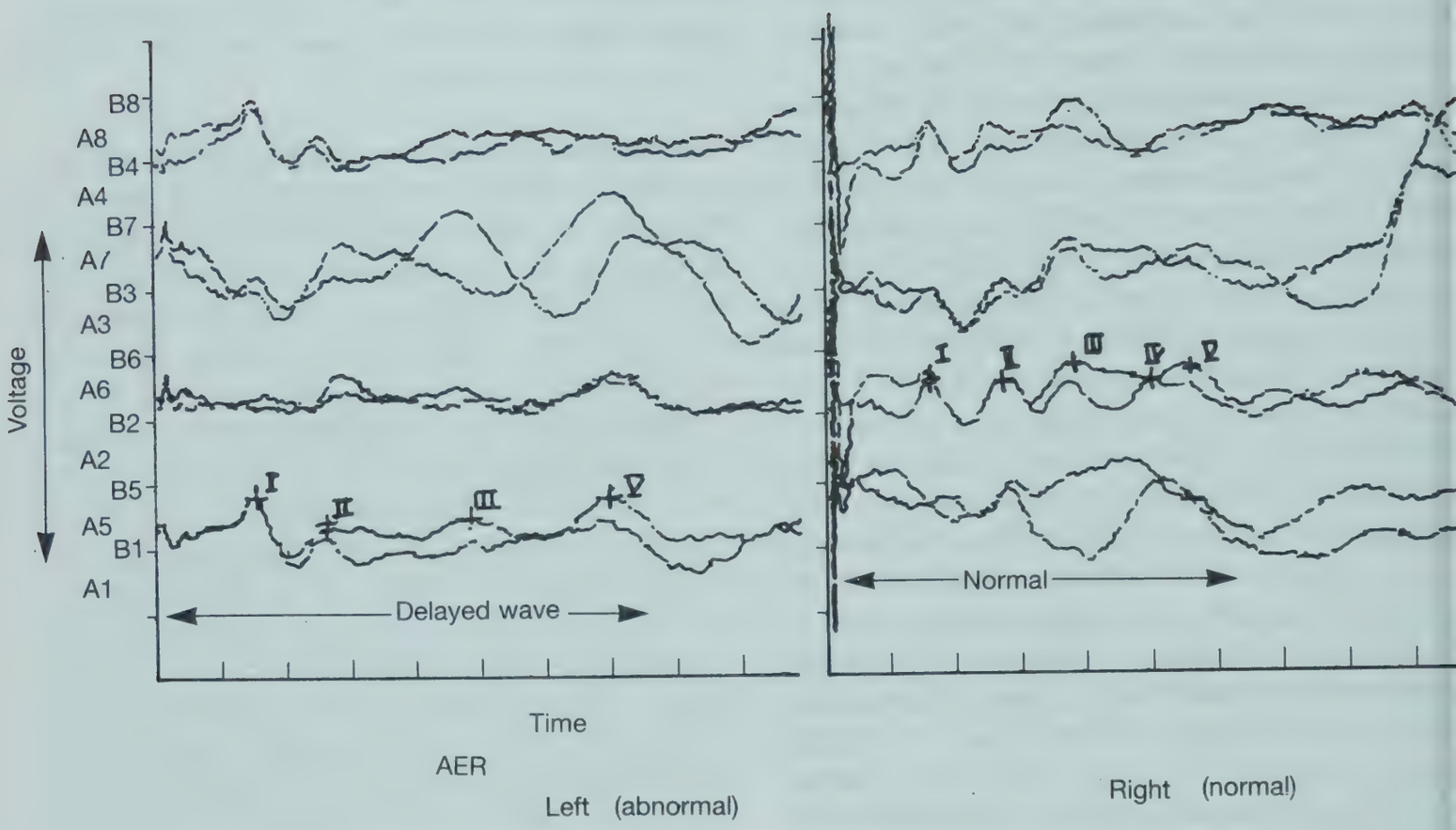


Fig 9.41a Brainstem auditory evoked responses in a patient with multiple sclerosis

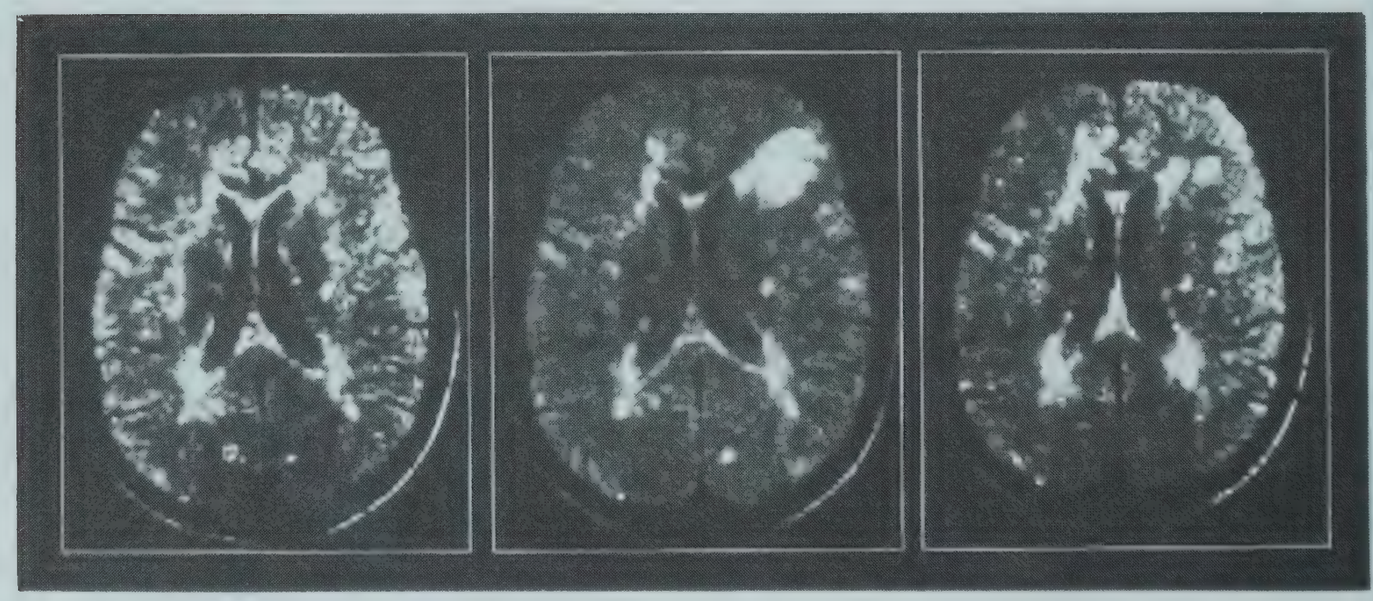
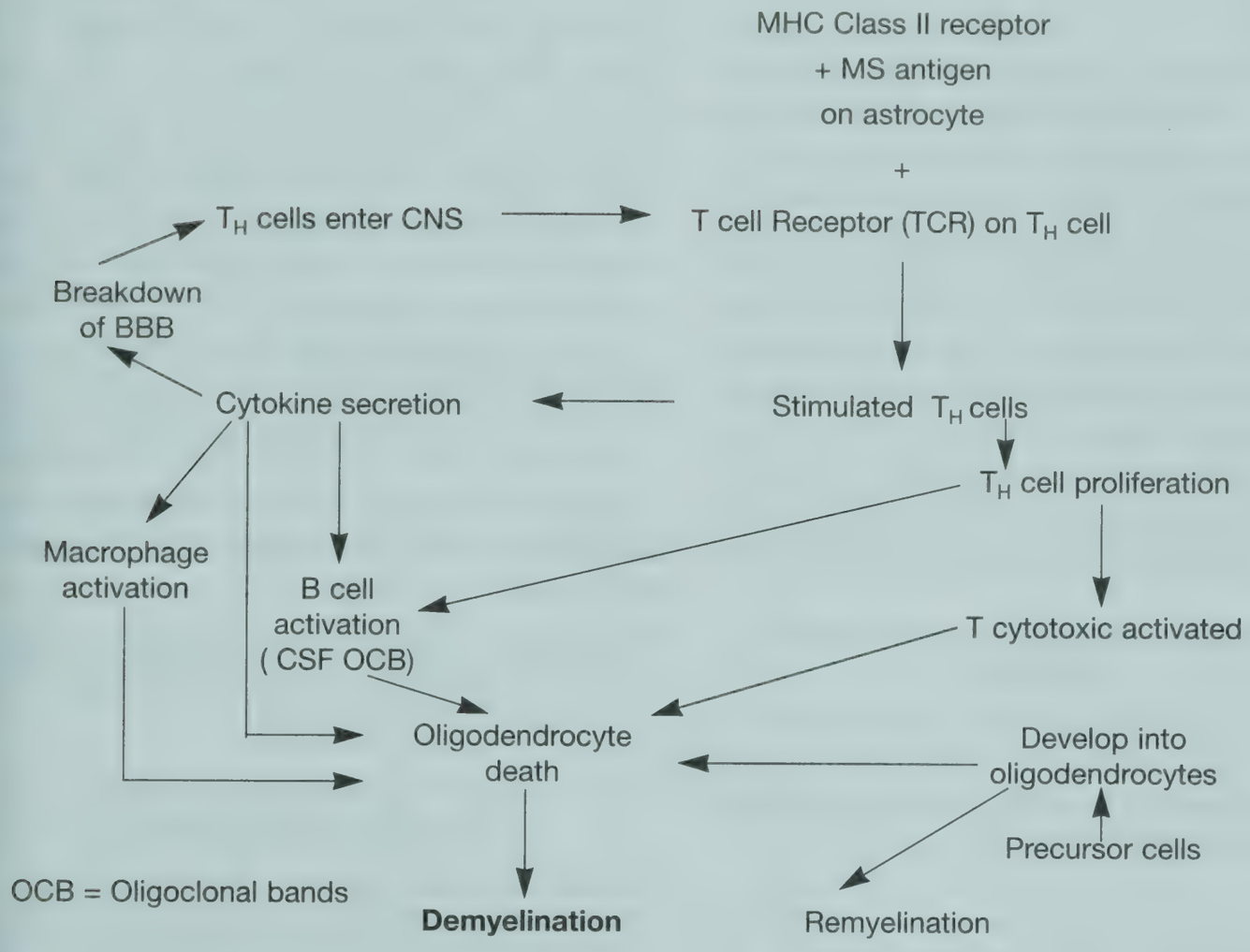


Fig 9.41b MRI in multiple sclerosis

Fig 9.42 Pathogenesis of multiple sclerosis



pain in multiple sclerosis often responds to carbamazepine, amitriptyline or a combination. Bladder dysfunction can be managed using fluid restriction, reflex stimulation, intermittent catheterisation and medications as required (alpha-adrenergic antagonists relax the external sphincter, cholinergic and anticholinergic drugs can stimulate or inhibit bladder contractions, respectively). Aids to mobility (crutches, wheelchair), compensators for impaired vision (such as large print or Braille books) and treatment of depression can all improve patient function.

Recovery from acute attacks: Corticosteroids have been used in an attempt to resolve an acute attack, particularly if vision is threatened. The specific agents which have been tried include oral prednisone (40–60 mg/day × 2 weeks), ACTH injections (40 units i.m. or i.v.daily × 5 days) and intravenous methylprednisolone (1 gram i.v. daily for 3 days). Intravenous 'pulse' dose methylprednisolone seems to be the most effective agent. Although the duration of optic neuritis is reduced, the ultimate extent of recovery may not be influenced. Trials suggest that oral steroids are useless and may even be harmful.

Altering the course of disease: Treatment modalities which have been tried include a variety of non-specific immunosuppressants as well as more specific agents. The non-specific agents tried include corticosteroids, continuous and 'pulse' cyclophosphamide, azathioprine, cyclosporin, and total lymphoid irradiation.

Intravenous methylprednisolone may decrease the frequency of recurrences of optic neuritis. Of the other non-specific immunosuppressants, azathioprine seems to be the least toxic and the most promising. However, the relatively more specific immunomodulator β-interferon (Betaseron, administered subcutaneously), is now the most widely used agent worldwide. It appears to increase the period between attacks in patients with relapsing-remitting pattern of disease and mild to moderate disability. The main side effect of this medication is a flu-like syndrome which responds to analgesics. Attempts to induce tolerance to the 'MS' antigen have lead to trials of 'copolymer 1'. This analogue of myelin basic protein is given subcutaneously and is undergoing clinical trials.

Acute Disseminated Encephalomyelitis (ADEM)

This is a monophasic illness characterised by multiple areas of demyelination within the brain and spinal cord. The pathogenetic mechanism is thought to be autoimmune.

Etiology Two broad categories of ADEM are defined: postvaccinal and postinfectious. The culprit vaccines are the Semple vaccine for rabies (1:5000 vaccinations) and the small pox vaccination (1:5000; no longer widely used). The infectious causes include measles, varicella and rubella.

Pathology ADEM is believed to be the human counterpart of experimental allergic encephalomyelitis (EAE), a model based on hypersensitivity to the myelin basic protein. The central nervous system shows numerous foci of perivenous lymphocytic infiltration and adjacent demyelination. Once the acute process subsides, some areas may be partly remyelinated.

Clinical features Clinical manifestations are protean. The usual course of the disease is worsening of neurologic symptoms over 1–4 weeks. The disease may present as an encephalitis (seizures and coma may occur), a non-compressive myelopathy, cerebellar ataxia (common after varicella) or with features of all three. Brainstem involvement may also occur but is less common. Chorea and athetosis are rarely seen. The cerebrospinal fluid shows lymphocytosis (50–200 cells/mm^3) and mild elevation of protein (<100 mg/dl). The CT scan may be normal, or may show areas of periventricular and spinal cord demyelination. There may be demyelination of peripheral nerves documented clinically or with nerve conduction studies. Forty per cent of patients recover completely, 20 per cent die. Differential diagnosis includes viral encephalitis, Reye syndrome as well as the first attack of multiple sclerosis.

Treatment ADEM is treated with a course of high dose steroids, although the efficacy of this treatment has been disputed.

Acute Necrotising Hemorrhagic Encephalomyelitis (ANHE)

ANHE is a neurologic disorder similar to ADEM except for a greater severity and a more rapid rate of progression. Death occurs in over 50 per cent of patients. Pathologically, there is perivenous accumulation of lymphocytes, macrophages and numerous polymorphonuclear white blood cells. There are perivenous foci of demyelination but these are dotted with small hemorrhages secondary to necrosis of the vessel wall. Cerebrospinal fluid examination may show a marked elevation of protein and polymorphonuclear pleocytosis of upto 2000 cells/mm. The differential diagnosis includes acute encephalitis, acute meningitis, multiple septic cerebral emboli and cerebral malaria.

HTLV-1 Associated Myelopathy (HAM)-Tropical Spastic Paraparesis (TSP)

HAM-TSP defines a syndrome of non-compressive myelopathy developing on a background of HTLV-1 infection. The typical

clinical picture is of a slowly progressive spastic paraparesis.

Etiology The HTLV-1 virus is a retrovirus like the HIV virus. In patients, the virus can be cultured from WBCs in the blood and CSF, antibodies are detected in the serum and CSF and electron microscopy shows the presence of virus particles in the spinal neurons. Some of the tissue damage is due to activation of the patient's immune response.

Pathology There is chronic inflammation of the meninges and demyelination of the lateral column of the spinal cord.

Epidemiology The syndrome of HAM was described from southern Japan and TSP from the Caribbean. Both conditions affect young adults. Transmission of the virus is by sexual contact, transplacental or blood transfusion. Not all infected individuals develop HAM-TSP. Some develop T cell leukemia and others remain asymptomatic.

Clinical features and differential diagnosis The patient presents with spastic paraparesis and may have back pain, paresthesiae and bladder dysfunction; in 50 per cent of patients there is sensory loss and rarely, a sensory level. Even in endemic areas cord compression should be excluded by imaging. If an MRI of the head is performed, periventricular demyelination may be seen and the CSF shows oligoclonal bands. However, unlike in multiple sclerosis the course is of steady disease progression and neurological lesions outside the cord are rare. AIDS and associated myelopathy may mimic HAM-TSP.

Treatment Steroids may be beneficial in HAM. Antiviral drugs are being evaluated.

KEY CONCEPTS

Multiple sclerosis

- Multiple sclerosis is a chronic relapsing-remitting demyelinating disease of the CNS; in the late stages the clinical course may be 'chronic progressive'. MS is probably the result of an autoimmune response to myelin components (myelin basic protein) that results in demyelination .
- Pathologically, MS is a disease of the white matter affecting the periventricular areas, optic nerves, the brainstem, the cerebellum, and the lateral and posterior spinal columns.
- There is a slight female preponderance. The onset of illness is typically between ages of 20 and 40 years. There is an increased prevalence in temperate regions.
- In about a fifth of patients onset is with visual symptoms: diminished vision due to *retrobulbar neuritis,* sudden onset of diplopia. Bilateral *internuclear ophthalmoplegia* (failure to adduct with preservation of other eye movements) is very suggestive of MS. Spastic paraparesis results from spinal cord involvement and can occasionally present as a transverse myelitis. Cerebellar involvement results in ataxia, scanning speech and an intention tremor (*Charcot's triad*). Additional features include Lhermitte's sign (shock-like sensation down the spine) and signs of Uhthoff's phenomenon (worsening with heat) and unexplained fatigue.
- A diagnosis of MS is suspected when there is a relapsing-remitting illness with multifocal involvement. The CSF is abnormal; oligoclonal IgG bands and myelin basic proteins are seen in the CSF. An MRI is the most sensitive test for the detection of demyelination plaques. A double dose CT scan is also reasonable. Evoked potentials may be abnormal.
- The management of MS includes supportive measures, treatment of spasticity (baclofen), intermittent self-catheterisation (for bladder symptoms) and rehabilitation. *Beta interferon* may modify the course of the relapsing-remitting illness. Intravenous methylprednisolone may hasten recovery.

Acute disseminated encephalomyelitis

- This syndrome is characterised by 'postinfectious (most often post-varicella) demyelination involving perivascular regions in the CNS. It is probably an autoimmune response to myelin triggered by the viral infection.
- The illness is monophasic (unlike MS). Multifocal signs involving the optic nerve, spinal cord, and brain (ataxia, confusion) are evident at the time of initial presentation.
- The CSF shows mononuclear pleocytosis.
- The treatment is mainly supportive. Intravenous methylprednisolone may help.

9.14 Congenital and metabolic diseases of the central nervous system

Mental Retardation

Mental retardation is defined by an intelligent quotient (I.Q.) less than 70 resulting from a pathophysiological process affecting the brain during its developmental period, from the in utero period to the fifth year after birth.

Epidemiology The prevalence of mental retardation is approximately 1 in 1000 live births. In roughly 50 per cent of cases no definite etiology can be assigned. The single most common genetic defect that causes mental retardation is the *fragile X syndrome.* Other common causes are Down syndrome, intrauterine exposure to injurious agents (infections, maternal alcohol or drug abuse, teratogenic drugs), birth trauma and thyroid hormone deficiency in the mother. Malnutrition rarely causes mental retardation unless it is severe.

Clinical features Severely retarded children (IQ <20) need help throughout their life with activities of daily living such as feeding and using the toilet. They never acquire language or motor milestones. With an IQ between 20–50, there is a delay in all developmental milestones but ultimately the individual can be trained to feed, toilet and dress himself. In this group prognosis depends on the presence or absence of associated behavioural problems. Some individuals (for instance those with Down syndrome) achieve a high level of social adjustment. Others may show hyperactivity, self-mutilation, destructive behaviour and have to be institutionalised. Those with an I.Q. between 50 and 70 may or may not be recognised as mentally retarded. They may be able to lead apparently normal productive lives in a sheltered setting.

Fragile X syndrome

This syndrome is characterised by increased fragility of the patient's X chromosome in a culture medium deficient in folic acid. A study of the abnormal chromosome has shown that there are an increased number of trinucleotide repeat sequence CGG. Individuals with more than 200 'repeats' manifest with mental retardation and those with 50–200 'repeats' are carriers. Although the disease is X chromosome linked, it can affect men and women. Study of the unusual genetics of the fragile X syndrome has led to the definition of a new pattern of genetic inheritance seen subsequently in at least four other neurologic disorders. The clinical features include prognathism (protrusion of the lower jaw), bat ears, and macroorchidism (large testes) in addition to the mental retardation.

Down syndrome

This syndrome has been discussed earlier and can present in adult life with a history of mental retardation. These adults are short, and have stigmata suggestive of Down syndrome. In mid-adult life most develop deterioration due to Alzheimer's disease.

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[1] These include Huntington's disease, spinocerebellar ataxia type 1, myotonic dystrophy and spinal bulbar atrophy (Kennedy's disease).

Cerebral palsy (Static encephalopathy)

About 1 in 1000 children is born with a motor and/or cognitive deficit. A variety of motor disorders can be seen. *Spastic diplegia* refers to weakness of all four limbs in which lower limb involvement is more marked than upper limb involvement in contrast to bilateral hemiplegia wherein the upper limbs are weaker. The patient has a stiff gait and the legs may cross: this is known as *scissors gait.*

Hemiplegia may develop during birth or within the first three years to qualify for a diagnosis of cerebral palsy. The limbs fail to grow normally. Cognitive deficits are uncommon but seizures occur in one-third of all patients.

An *extrapyramidal syndrome* with choreoathetosis appears to result from kernicterus in the perinatal period. Such children are severely retarded and deaf.

The principle of management is to ensure that there is no treatable lesion and for this a CT scan, EEG and, sometimes, tests for inherited metabolic disorders need to be done. As the child grows, symptoms may change although the lesion remains static. Supportive therapy includes hearing aids, speech therapy, medication for seizures or hyperactivity, physiotherapy and orthotic devices, such as, leg braces, and in some patients, surgery. Surgical measures include relieving contractures, correcting scoliosis and dorsal rhizotomy, that is interrupting the spinal reflex arc to relieve spasticity.

ABNORMALITIES OF CEREBROSPINAL FLUID DYNAMICS

The average intracranial volume in an adult is about 1700 ml with approximately 1400 ml being occupied by the brain parenchyma. The rest is taken up by the blood (150 ml) and the cerebrospinal fluid (150 ml). In an adult, this intracranial volume cannot expand and hence an increase in volume of any one of the three constituents must be accompanied by a decrease in volume in the other two. This has been termed the *Munro-Kelly doctrine.* Because intracranial volume is fixed, any increase in the volume of the structures within results in a sharp rise in intracranial pressure.

Cerebrospinal fluid (CSF) is formed at the choroid plexuses which are found in the lateral ventricles, the roof of the third ventricle and the fourth ventricle. It is absorbed by the arachnoid granulations over the cerebral convexity and thereby returned to the blood stream through the dural sinuses. The direction of CSF flow is from the lateral ventricles into the third ventricle through the *foramina of Munro,* from the third ventricle to the fourth ventricle through the *aqueduct of Sylvius* (*iter*) and from the fourth ventricle into the subarachnoid space through one medial and two lateral foramina called the *foramina of Magendie* and *Luschka,* respectively. The normal rate of formation of the CSF is 20 ml/hour (or 500 ml/day) so that the entire volume of CSF is recycled about four times each day.

Hydrocephalus

Hydrocephalus refers to an increase in the amount of CSF within the ventricular system resulting in ventricular dilatation. Hydrocephalus is typically associated with an increase in the normal intraventricular pressure. There is a subset of patients, usually elderly, in whom there is no elevation of intracranial pressure. This subset is called *normal pressure hydrocephalus* and the mechanism is thought to be due to impaired CSF absorption. An increase in the rate of formation of CSF is rarely the cause of hydrocephalus (seen with choroid plexus papillomas). More commonly, there is an obstruction somewhere along the CSF pathway. If the obstruction is proximal to or at the foramina of Luschka and Magendie, the resultant hydrocephalus is called a *non-communicating hydrocephalus.* If there is an obstruction in the basal cisterns, at the foramen magnum or over the cerebral convexity, or if the

rate of CSF resorption by the arachnoid villi is reduced, the resulting hydrocephalus is termed a *communicating hydrocephalus.*

The causes of a non-communicating hydrocephalus are an obstruction within the ventricular system (such as intraventricular cysticercus, colloid cyst), an extrinsic distortion of the ventricular system (such as tumour, hemorrhage, head injury, edema around an inflammatory lesion), or a congenital abnormality of the ventricular system. Common types of congenital abnormalities are *aqueductal stenosis, Dandy-Walker syndrome* (absent foramina of Magendie and Luschka) and the Arnold-Chiari malformation (displacement of the cerebellar tonsils into the cervical spinal canal). The usual cause of a communicating hydrocephalus is an inflammation of the meninges as a sequelae of subarachnoid hemorrhage, chronic meningitis or meningoencephalitis.

In an infant, hydrocephalus presents as delayed closure of the fontanelle, increase in head circumference, developmental delay and, later, as poor feeding and altered sensorium. At this stage, a characteristic sign (secondary to pressure on the mesencephalic tegmentum) is the so-called *setting sun sign*: the upper eyelids are retracted and the two eyeballs rolled downwards and inwards as though the child is staring at his nose. If the increased CSF pressure is released, this sign disappears. Patients with incomplete aqueductal stenosis may remain asymptomatic through childhood and then decompensate in adult life following a minor head injury, stroke or without any apparent cause. In an adult patient, acute onset hydrocephalus presents with headache and altered sensorium. Signs which may be present include bilateral extensor plantar responses, frontal release reflexes, bilateral sixth cranial nerve palsies, papilledema and a sluggish pupillary response. In chronic hydrocephalus, there is headache, dementia, an unsteady gait, and urinary incontinence. Papilledema is present except in cases of normal *pressure hydrocephalus.*

The diagnosis is made by an imaging study, either a CT scan or an MRI scan. It should be remembered that ventricular size can increase with normal ageing or in response to atrophy of the surrounding brain. This would not represent hydrocephalus. An inability to visualise cortical sulci, enlargement of the temporal horns, a change in shape (rounding) and an increase in the angle between the frontal horns and the presence of periventricular lucencies (on CT) or hyperintensities (on MRI) suggest true hydrocephalus. If the obstruction is at the foramen of Munro, a single lateral ventricle will be enlarged. Aqueductal stenosis results in enlargement of both the lateral ventricles and the third ventricle, but not the fourth ventricle. In the Dandy-Walker syndrome, all the four ventricles are enlarged and the cerebellar hemispheres are hypoplastic.

Another investigation which is occasionally performed in patients with hydrocephalus (especially in those with normal pressure hydrocephalus) is isotope cisternography. This test will show reflux of isotope from the subarachnoid space into the ventricular system in patients with communicating hydrocephalus. In patients with hydrocephalus following meningitis, a lumbar puncture may be performed (after a CT scan has excluded non-communicating hydrocephalus)[1] to exclude residual inflammation prior to shunt treatment.

In acute hydrocephalus, an emergency treatment is ventricular 'tapping' or making a burr hole to relieve intracranial pressure. In chronic hydrocephalus, the most effective treatment is 'shunting' the excess CSF into the right atrium (ventriculoatrial shunt) or the peritoneal cavity (ventriculoperitoneal shunt). Delayed complications of shunt procedures include shunt obstruction and infection within the shunt. A portion of the shunt runs

[1] A lumbar puncture in non-communicating hydrocephalus can result in fatal herniation.

subcutaneously over the cranial vault and laterally in the neck. If the patient has recurrent symptoms, shunt function can be checked in this area.

Idiopathic Intracranial Hypertension (Benign Intracranial Hypertension or Pseudotumour Cerebri)

This is a syndrome of raised intracranial tension due to an unknown cause. The typical patient is an obese young woman who presents with severe bilateral headaches. Fundus examination shows papilledema and a CT scan of the head is obtained with the suspicion of an intracranial space occupying lesion. The CT scan shows no 'mass' lesion, and normal or decreased ventricular size. This diagnosis should not be made until a mass lesion and cortical venous obstruction have been ruled out by imaging studies. The diagnosis is confirmed by a lumbar puncture, which shows biochemically and cytologically normal CSF at an increased pressure (>200 mm of water).

In most patients there is no obvious underlying cause. In a few patients, drugs (high doses of vitamins A or D, tetracycline) or endocrine abnormalities (hyperparathyroidism, Cushing syndrome) may be responsible. The greatest danger to the patient is loss of vision. This is usually preceded by warning symptoms in the form of transient visual obscurations.

Treatment modalities include periodic spinal 'tapping' (removal of about 50 ml of CSF at each tap), prednisone (40–60 mg/day), acetazolamide to reduce CSF formation (500 mg 2–3 times a day) and weight reduction. If all these measures fail, *thecoperitoneal* shunting and optic nerve decompression have been tried in patients who are losing vision.

ANOMALIES OF THE CRANIOVERTEBRAL JUNCTION

Anatomy and embryology The craniovertebral junction consists of the inferior portion of the occipital bone and the first two cervical vertebrae which together form a funnel-shaped structure, held together by ligaments, and housing the caudal portions of the medulla and cerebellum and the most cranial portion of the cervical spinal cord. The first cervical vertebra is called the *atlas* vertebra. The atlas, unlike other vertebrae, does not develop a vertebral body and looks like a ring with two lateral extensions, the lateral masses on which the occipital condyles of the occipital bone sit. This is a weight-bearing joint known as the (atlanto-occipital joint), and has little mobility. The second cervical vertebra is the *axis*. The body of the axis fuses with the embryological portion of the body of the atlas to form a superior extension, the *odontoid process* or *dens*. The odontoid serves as a pivot and the atlas and skull together rotate around the axis to enable rotatory neck movements.

Anomalies Normally the base of the occipital bone is convex downwards. In *basilar impression* there is, instead, an invagination, that is, an upward indentation of the skull base around the foramen magnum. Typically this is seen in conditions which impair normal ossification of the occipital bone such as, osteomalacia, osteogenesis imperfecta, cretinism and rickets as well as acquired bone disease (Paget's disease). The weight of the skull presses downward, the cervical spine is relatively more rigid and hence the base of the occipital bone bends upwards. This condition is not seen in infants who are not yet walking (an erect posture is required). Basilar invagination narrows the foramen magnum.

Platybasia refers to an increase in the angle between the floor of the anterior cranial fossa and the plane of the clivus (Fig 9.43). This angle is normally less than 147 degrees. Platybasia is often seen along with basilar invagination but causes no symptoms.

Occipitalisation of the atlas is the fusion of a part, usually anterior, or all of the atlas with the occiput.

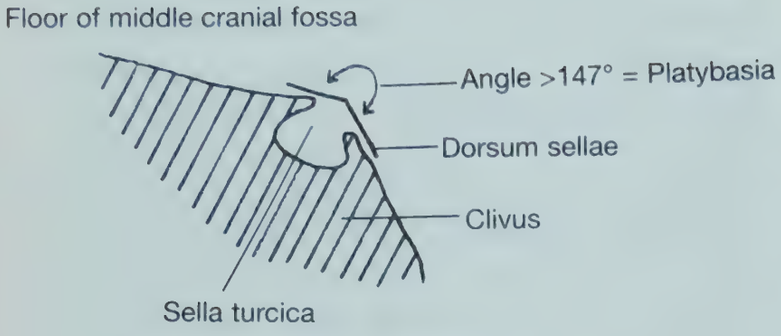

Fig 9.43 Platybasia

Klippel-Feil anomaly and short neck are defined in the section on syringomyelia. The second and third cervical vertebrae may be fused even in the absence of a Klippel-Feil anomaly.

The space available for the cervicomedullary junction consists of the distance between the posterior margin of the dens anteriorly and the posterior lip of the foramen magnum posteriorly. If this distance is less than 19 mm in an adult, neurological symptoms are likely. The odontoid process is held against the anterior arch of the atlas by the transverse odontoid ligaments. If these ligaments are congenitally hypoplastic or become relaxed following local inflammation, the dens can move posteriorly compressing neural structures. Inflammatory processes responsible include tuberculous and bacterial osteitis, rheumatoid arthritis and sometimes, even acute pharyngitis. Part or all of the odontoid process may be developmentally separate or may become separated following trauma. This again renders the craniovertebral junction unstable.

Radiology On a normal frontal skull X-ray the Fischgold's bimastoid line joining the two mastoid tips, passes through the atlantooccipital joint and touches the upper tip of the odontoid process. In basilar invagination these structures are above this line. On a lateral view the tip of the odontoid lies above a line joining the posterior lip of the foramen magnum to the posterior tip of the hard palate (Chamberlain's line) and is more than 4.5 mm above a line (known as McGregor's line) joining the same point on the hard palate to the most caudal point on the occipital bone.

Atlantoaxial dislocation An injury in this location can cause medullary damage and immediate death. If there is only an instability without a dislocation, a patient may be asymptomatic initially, and then develop symptoms over time as repeated flexion-extension movements of the spine cause progressive damage to the cervical spinal cord. Patients with congenital or acquired atlantoaxial instability are particularly susceptible to dislocation. Typically, patients are young children or elderly patients with bone or joint disease. There may be occipital pain due to compression of the C2 nerve root. The patient may hold his head gingerly or at an angle and may support the chin whenever movements of the head are required. He may prefer to turn the whole body rather than the head. There may be subtle upper motor neuron signs in all four limbs. Paresthesiae in the fingers or wasting of the small muscles of the hand may be seen due to pressure on the anterior spinal artery causing an ischemia in the watershed zone (C8–T4) between this artery and the artery of Adamkiewicz. In this situation, a minor injury may result in devastating quadriparesis or death. An MRI is the diagnostic modality of choice. A plain X-ray may be normal. Flexion-extension views are more likely to show an abnormality but may also precipitate quadriparesis and hence should be taken with great caution.

The treatment is surgical (laminectomy and fusion) followed by a stabilising Minerva cast and then a cervical collar.

Foramen Magnum Tumours

A compressive lesion in this location causes quadriparesis with a Horner syndrome and occipital pain. A classic pattern that is

sometimes seen is the sequential involvement of one shoulder and arm followed by weakness of the ipsilateral leg, the contralateral leg and then the contralateral arm as the tumour starts laterally and extends to the opposite side.

Neurocutaneous Syndromes (Phakomatoses)

These are clinically distinct, genetic disorders affecting the skin and nervous system.

Neurofibromatosis type 1 (von Recklinghausen's disease)

This is an autosomal dominant inherited disorder and the disease has been linked to an abnormality of the nerve growth factor gene on chromosome 17. The nerve growth factor has maximal effect on the growth of Schwann cells and neurons in the sympathetic ganglion in animal experiments. There are mutiple hamartomas. The somatic markers of the disease are: 1) hyperpigmented lesions of 0.5 to 2 cm diameter (cafe-au-lait spots)[1], 2) subcutaneous, mobile and usually painless nodules (neurofibromas), 3) iris nodules (Lisch nodules), and 4) areas of failed ossification seen on the limb X-ray (pseudoarthroses). Involvement of the nervous system may manifest as an acoustic nerve schwanomma (cerebellopontine angle syndrome), spinal cord neurofibroma, meningiomas which may be multiple, aqueductal stenosis resulting in obstructive hydrocephalus, optic nerve glioma or as a glioblastoma. The involvement of other systems may include renal hamartomas and pheochromocytoma. The treatment is directed at the symptomatic lesions and is lesion specific. The development of tumours cannot be prevented; regular annual clinical evaluation, or at the onset of symptoms is the answer to early detection of tumours.

Neurofibromatosis type 2

This is an autosomal dominant disorder (gene on chromosome 22) in which acoustic nerve schwannomas develop, usually on both sides. Meningiomas and astrocytomas may also develop but there are no extracranial manifestations.

Tuberous sclerosis

This is an autosomal dominant disorder linked to a mutant gene on chromosome 9. The clinical manifestations are mental retardation and intractable seizures. There are pathognomic skin lesions called ash-leaf macules (hypo-pigmented leaf shaped areas), adenoma sebaceum (angiofibroma seen as small white papules over cheeks and forehead) and a shagreen patch (large area of rough, raised, yellowish skin over lower back). There may be hamartomatous tumours in the heart (rhabdo-myoma) and other organs (angioleiomyoma). On imaging studies multiple, calcified nodules in the subependymal region are seen. The EEG is abnormal.

Other syndromes

The *Sturge-Weber syndrome* is characterised by a facial port-wine nevus (in the distribution of the ophthalmic division of the trigeminal nerve) and occipital venous hemangioma. The cortical vascular malformation is seen on imaging as 'railroad track calcification' and may cause seizures. Less commonly, there is contralateral hemiparesis.

The *von Hippel-Lindau disease* is an autosomal dominant syndrome linked to chromosome 3. The clinical features are retinal and cerebellar hemangiomas and polycystic kidneys.

Ataxia telangiectasia is an autosomal recessive disorder characterised by oculocutaneous telangiectasia, cerebellar ataxia, chorea and humoral immunodeficiency resulting in frequent infections.

The *Sjogren-Larsson syndrome* is an autosomal recessive disorder with spastic paraparesis, generalised icthyosis, retinitis pigmentosa and mental retardation.

[1] The cafe-au-lait spot may be present in the same dermatome as spinal neurofibroma.

INHERITED METABOLIC DISORDERS PRESENTING AS NEUROLOGIC SYNDROMES

There is a large variety of inherited metabolic disorders and recent advances in biochemistry and genetic testing that enable us to diagnose a number of these conditions. However, the treatment of these disorders is still in its infancy. Bone marrow transplantation and gene therapy using viral vectors have been attempted as techniques to restore adequate levels of the defective enzyme or protein. Such therapies are experimental. Prominent exceptions to this therapeutic nihilism are Wilson's disease in which chelating agents are used and phenylketonuria and Refsum's disease in which dietary modifications can prevent symptoms.

The variety of inherited disorders has been briefly discussed in the section on endocrinology and metabolic disorders. Most of these diseases present in infancy or childhood. Two broad patterns are recognised. In one set of disorders there is more prominent grey matter involvement. These conditions are called the *poliodystrophies.* They present with progressive dementia, seizures, myoclonus and retinal lesions (such as a 'cherry red spot' on the retina). Examples of this group include Tay-Sach's disease, Neimann-Pick disease, Gaucher's disease and subacute necrotising encephalopathy (*Leigh's disease*). All these conditions may rarely begin in adult life.

The other broad category is predominant involvement of the white matter resulting in long tract signs (spasticity, cerebellar signs, sensory ataxia), and optic atrophy. This group of conditions are called *leukodystrophies.* Some examples which may begin in adult life in rare cases are adrenoleukodystrophy, metachromatic leukodystrophy and globoid cell leukodystrophy (Krabbe's disease). The MRI in all these conditions will show bilateral large confluent areas of subcortical demyelination. In adrenoleukodystrophy there may be adrenal hypofunction. A predominantly spinal and neuropathic form of this illness has been described (*adrenomyeloneuropathy*).

Syndromes of myoclonic epilepsy with dementia and cerebellar ataxia are called 'progressive myoclonic epilepsies'.

Mitochondrial Encephalomyopathies

This is a diverse group of disorders that have in common functional, structural or genetic abnormalities of the mitochondria. Each of these diseases is a relatively rare entity. The genetic defect may be in the mitochondrial DNA in which case inheritance is exclusively maternal, or in that part of the nuclear DNA which regulates the synthesis of mitochondrial enzymes. The common neurologic manifestations are myopathy, chronic progressive external ophthalmoplegia (pupils are spared), sensorineural deafness, optic neuropathy, retinitis pigmentosa, cerebellar ataxia, stroke, dementia, seizures and myoclonus. These features may occur in various combinations. There may also be involvement of other organs such as the heart. *Kearns Sayre* syndrome is characterised by ophthalmoplegia, pigmentary retinopathy, cardiac conduction defect, raised CSF protein and cerebellar ataxia. Patients may present with optic neuropathy alone (*Leber's optic atrophy*) or progressive ophthalmoplegia alone. In the latter case, the initial diagnosis may be myasthenia but the symptoms will not improve with anticholinesterases. The diagnosis of a mitochondrial disorder may be made in a muscle biopsy (ragged red fibres), with measurement of serum or CSF lactate (levels are elevated). In Leber's optic atrophy the genetic mutation is known and DNA studies on the peripheral blood can establish the diagnosis.

METABOLIC ENCEPHALOPATHY

Metabolic encephalopathy refers to a global disruption of cerebral function secondary to disturbances of the 'milieu interior'. A global

dysfunction may be the effect of an exogenous toxin, or due to a systemic illness or secondary to a diffuse CNS infection (such as viral encephalitis or meningitis), or due to raised intracranial tension (for example, secondary to a structural lesion in a so-called 'silent area' such as the frontal lobe). The first two etiologies define a subset of global brain dysfunction described as 'metabolic encephalopathy'.

Etiology 1. Electrolyte imbalances: Hyponatremia, hypernatremia, hypokalemia and hypercalcemia.
2. Endocrine disorders: The commonest endocrine causes are those secondary to diabetes mellitus such as ketoacidosis, non-ketotic hyperosmolar coma and hypoglycemia. Other causes include hypothyroidism (myxedema coma) and less commonly hyperthyroidism, Cushing's disease, therapeutic glucocorticoid administration, and Addison's disease.
3. Organ failure: Hepatic encephalopathy, both acute and chronic; uremic encephalopathy (renal failure); hypercapnic and anoxic-ischemic encephalopathy (cardiopulmonary failure).
4. Nutritional encephalopathies: In vitamin deficiencies such as deficiency of B_{12}, thiamine, niacin and pyridoxine.
5. Toxic encephalopathies: Alcohol (Wernicke-Korsakoff psychosis); other toxins including organophosphorus, arsenic, lead, narcotics, carbon monoxide, barbiturates.

Some of the common causes are discussed below.

Hypoxic Encephalopathy

Hypoxic encephalopathy is caused by insufficient oxygen reaching the brain as a consequence of circulatory failure, respiratory failure or both. Clinical conditions which may result in this type of brain damage are the causes of circulatory failure (cardiac arrest, myocardial infarction, shock), drowning, aspiration, respiratory muscle paralysis, prolonged seizures, strangulation and hanging and carbon monoxide poisoning.

Clinical features Mild hypoxia causes impaired judgement and muscle incoordination. Within a minute of cardiac arrest consciousness is lost. If circulation is restored within 4 minutes, complete recovery is possible. Hypoxia which does not at any time cause unconsciousness rarely causes permanent damage. The comatose patient gradually slips into progressively deeper stages of coma which may lead to death. In patients who suffer severe brain damage before cardiorespiratory function is restored, the sequelae may include a persistent vegetative state, myoclonic jerks, dementia, choreoathetosis and cerebellar ataxia.

Pathology The portions of the brain most susceptible to ischemia are the circulatory watershed areas the (parietooccipital lobes and globus pallidus), and certain neuronal types, such as, the hippocampal neurons and cerebellar Purkinje cells.

Management The diagnosis depends on the history of a hypoxic or ischemic event. The documentation of a low arterial blood PO_2 or sustained severe hypotension (systolic blood pressure below 70 mmHg) during the acute episode help substantiate the diagnosis. In carbon monoxide poisoning, a cherry red colour of skin may be seen in light-skinned individuals for a few hours after the insult. There is no specific treatment to revert the neuronal damage. Supportive care measures should be instituted (see section on coma). Prevention consists of minimising the period of cardiorespiratory insufficiency by rapidly instituting resuscitation.

Acute Hepatic Encephalopathy

Acute hepatic encephalopathy occurs in patients with fulminant hepatic failure due to viral hepatitis, decompensated hepatic cirrhosis, drug-induced hepatitis or due to toxic injury to the liver.

Pathology and pathogenesis The characteristic neuropathologic finding is a large number of 'plump' astrocytes called protoplasmic astrocytes or Alzheimer Type II cells in the deeper layers of the cerebral cortex and in the lenticular nuclei. The neurons themselves look intact.

There are several theories of pathogenesis. Hepatic encephalopathy can be precipitated by increased intake of dietary protein or by a gastrointestinal hemorrhage, which also increases proteins in the bowel lumen. Microorganisms in the gut break down the amino acids formed by protein digestion to release ammonia which enters the portal circulation. In hepatic cell failure, the liver is unable to convert this ammonia to urea. It is thought that high levels of serum ammonia may affect brain function. Other metabolites which may contribute to hepatic encephalopathy include mercaptans, short chain fatty acids, and excess concentration of GABA in the central nervous system and an alteration of the ratio of aromatic to branched chain amino acids.

Clinical features In the initial stages, there is mental confusion along with signs of hepatic cell failure (icterus, ascites, etc.). The patient shows characteristic lapses in sustained muscle contraction (asterixis)[1]. Later the patient lapses into coma.

Investigations The EEG shows bilaterally synchronous slowing to 2–4 Hz (delta activity) background activity. In the frontal region there are prominent triphasic waves. Seizure activity may be noted. Serum ammonia levels are elevated. Liver function tests are deranged depending on the underlying etiology of hepatic dysfunction.

Management Treatment consists of restriction of dietary protein, mechanical cleansing of the gut (bowel wash twice daily), oral antibiotics (neomycin or ampicillin[2]) and lactulose (30 ml qid, dose adjusted to maintain 3–4 soft stools daily). Therapeutic modalities of uncertain efficacy include levodopa, bromocriptine, intravenous infusions of branched chain amino acids, flumazenil, sodium benzoate and hemoperfusion.

Wernicke-Korsakoff Syndrome

Wernicke's encephalopathy is an acute onset clinical syndrome characterised by confusion, oculomotor paralysis and gait ataxia. As the patient recovers, the eye movements and gait become normal and the patient is left with a syndrome of profound anterograde amnesia and normal intelligence– the *Korsakoff psychosis*.

Etiology The cause of the syndrome is thiamine deficiency. It is usually seen in alcoholics since their nutritional status is precarious and metabolism of alcohol increases the body's need for thiamine.

Clinical features The most characteristic signs are the eye signs which may be very varied. There may be bilateral sixth nerve paresis, horizontal and vertical gaze evoked nystagmus, and supranuclear gaze palsies. In extreme cases eyeballs are frozen and the pupils are miotic. There is truncal cerebellar ataxia or gait ataxia. There is a drowsy apathetic state. Twenty per cent show signs of alcohol withdrawal. The amnesia of Korsakoff's psychosis is permanent in 80 per cent.

Pathology Necrosis, vascular proliferation and hemorrhage are seen in the periventricular portions of the mammillary bodies, hypothalamus, thalamus, midbrain (periaqueductal gray) and fourth ventricle.

[1] The patient is asked to hold his upper limbs in front in an extended position with the hands dorsiflexed at the wrist and to sustain this posture. There are brief lapses of muscle tone which are voluntarily corrected by the patient, resulting in a 'flapping' movement.

[2] Ampicillin is preferred as small amounts of neomycin may be absorbed resulting in renal toxicity.

Treatment Treatment should be initiated as soon as possible. Fifty mg of thiamine is administered intravenously and 50 mg intramuscularly every day until the patient resumes a normal diet. Supportive care is provided.

Other causes of metabolic encephalopathy are discussed under the respective sections.

KEY CONCEPTS

Craniovertebral junction anomalies

- A number of developmental anomalies of the skull base and upper cervical spine can result in a reduction in the space available for the lower brainstem and the cervical spinal cord; this results in symptoms of compression of the cervical spine, medulla and cerebellum.
- *Platybasia* is a flattening of the skull base with the angle between plane of the clivus and anterior fossa exceeding 147°. *Basilar invagination* is the protrusion of the odontoid into the foramen magnum; patients have a short neck and multiple signs of brainstem and cord compression. *Arnold-Chiari malformation* results in elongation of the cerebellar tonsils which protrude through the foramen magnum. *Klippel-Feil* anomaly is characterised by fusion of the cervical vertebrae. *Atlantoaxial dislocation* is often precipitated by an innocuous injury as a result of which the atlas is displaced anteriorly relative to the axis.
- The symptoms and signs of CV junction anomalies are due to compression of various tracts: varying degrees of quadriparesis with spasticity and hyperactive tendon reflexes. Dysarthria and dysphagia may result from brainstem and lower cranial nerve compression. There may be lower motor neuron signs in the upper limbs (e.g., wasting of the small muscles of hand).
- The diagnosis is by X-rays of the CV junction and CT/MRI scans.
- The treatment consists of stabilising the neck and avoiding excessive neck movements until clinical and radiologic assessment is completed. Surgical decompression is indicated for patients with progressive neurologic signs.

Neurofibromatosis

- This is an autosomal dominant disease characterised by hyperplasia and neoplasia of neuroectodermal tissue.
- There are two types. *Type I* neurofibromatosis (gene on chromosome 17) characterised by *cafe-au-lait* macules, freckles, *Lisch nodules* in the iris, plexiform neurofibromata, optic nerve glioma, osseous dysplasia and meningiomas or neurinomas; features of *type II* neurofibromatosis (gene on chromosome 22) include the development of bilateral acoustic neuromas and an onset of symptoms by the age of 20 years.
- The diagnosis is clinical. CT/MRI scans may be obtained for detecting intracranial tumours.

Tuberous sclerosis

- This autosomal dominant syndrome is characterised by mental retardation, epilepsy, facial *adenoma sebaceum*. There is an increased incidence of glial nodules, retinal hamartomas, cysts in the kidney, *ash-leaf* depigmented macules, *shagreen patches*. Two types are described: TS 1 is due to a gene on chromosome 9, while TS 2 is the result of a gene on chromosome 16.
- The diagnosis is clinical.
- Management consists of counselling and administering anticonvulsants for seizures.

Sturge-Weber syndrome

- This syndrome is characterised by facial *port wine* vascular nevus in the distribution of the ophthalmic division of the fifth nerve
- Other components of the syndrome include ipsilateral leptomeningeal angiomas and choroidal angiomas (these result in glaucoma). There may be muscular weakness and diminished growth of the contralateral side.
- The diagnosis is clinical; an X-ray skull shows *tram track* curvilinear calcification.
- There is no specific treatment.

Ataxia telangiectasia

- This autosomal recessive disorder is characterised by oculocutaneous telangiectasia, cerebellar ataxia and recurrent sinopulmonary infections. There is an increased risk of lymphoid neoplasms. The DNA repair mechanism is defective.

9.15 Tumours of the nervous system

Classification Tumours of the nervous system may arise from the glial or neuronal elements of the brain or spinal cord or from the meninges, nerves and blood vessels. These tumours may be primary or secondary, that is, due to metastatic dissemination from a primary tumour elsewhere. Generally, metastatic tumours are more common than primary tumours. In this section, we will only discuss primary tumours of the nervous system. A classification of primary nervous system tumours is presented in Table 9.37. These tumours are further divided (based on histologic criteria for degree of malignancy) into low-, high-grade, and anaplastic types.

Epidemiology The incidence of brain tumours is estimated to be about 5 per 100,000 population. Two distinct peaks of incidence are seen: one in childhood (3–12 years) and another in adults (55–65 years). Brain tumours are more common in children, in whom they represent the most common solid tumour and the second most common malignancy (after leukemia). In children a majority of the tumours are infratentorial in location, whereas in adults the majority are supratentorial.

Low-grade gliomas are more common in the young whereas high-grade gliomas are more common in the elderly. Meningiomas and pituitary adenomas are more common in women while gliomas exhibit a slight male predominance.

Etiology The etiology of brain tumours is not fully known. A few risk factors, however, have been recognised. Cranial irradiation for leukemia and other intra- and extracranial cancers increases the risk of brain tumours. A majority of radiation-induced tumours are meningiomas, astrocytomas and glioblastomas. Infection with the human immunodeficiency virus (HIV) predisposes to the development of primary central nervous system lymphomas. Although the vast majority of brain tumours are not hereditary, a few inherited diseases do predispose to brain tumours. These include neurofibromatosis (Type 1 is associated with gliomas, meningiomas, schwannomas and Type 2 with ependymomas), tuberous sclerosis and von-Hippel-Lindau syndrome (hemangioblastomas). Retinoblastomas may be familial.

Acquired genetic abnormalities have been noted in brain tumours. This usually involves the loss or mutation of a tumour suppressor gene (such as the p53 gene or the retinoblastoma gene [Rb gene on short arm of chromosome 6]) resulting in the amplification of oncogenes.[1]

Pathogenesis and clinical features Unlike tumours elsewhere, brain tumours tend to present fairly early because they are often strategically located; dysfunction of a part of the nervous system may not be compensated by the

[1] Mutation in the p53 gene occurs in 40% of astrocytomas whereas overexpression of the epidermal growth factor receptor is seen in 40% of patients with glioblastoma multiforme.

Table 9.37 Classification of primary tumours of the nervous system

1. Neuroectodermal tumours
   - A. Glial cell origin (Gliomas)
     - Glioblastoma multiforme
     - Astrocytoma
     - Oligodendroglioma
     - Ependymoma
     - Papilloma of the choroid plexus
   - B. Neuronal origin
     - Medulloblastoma
     - Ganglioneuroma
   - C. Pineal cell origin
     - Pineocytoma
     - Pineoblastoma
2. Mesodermal tumours
   - Meningioma
   - Sarcoma
3. Nerve sheath tumours
   - Neurilemmoma (Schwannoma)
   - Neurofibroma
4. Tumours due to maldevelopment
   - Craniopharyngioma
   - Teratoma
   - Hamartoma
   - Chordoma
   - Germ cell tumours
5. Tumours of vascular origin
   - Hemangioblastoma
6. Tumours of the anterior pituitary
7. Miscellaneous and unclassified (e.g. primary CNS lymphoma)

rest, unlike other organs. The other reason is that there is only a limited space within the cranium for them to grow large. Generally speaking, children tend to have more severe symptoms and present early because of a greater frequency of infratentorial tumours.

The symptoms of brain tumour may thus be related to increased intracranial pressure (generalised symptoms common to several tumours), or due to localised dysfunction of the involved part (specific to tumour location and type). An increase in intracranial pressure is due to the mass itself, associated peritumoral edema, obstructive hydrocephalus (interference with the circulation of the CSF) or due to vascular engorgement. The 'mass effect' and the edema vary depending on the tumour size, its rate of growth and the histology. Some, of these factors may be interrelated: high grade gliomas grow more and provoke severe edema, whereas low grade gliomas or meningiomas scarcely produce any brain swelling. An important factor in the genesis of cerebral edema is that the tumour neovessels do not possess a blood-brain barrier.

Consequently, plasma proteins and water extravasate through tight junctions of the capillary endothelium into the extracellular space resulting in a *vasogenic cerebral edema.*[1] Ventricular obstruction is more likely with posterior fossa tumours and periventricular and intraventricular tumours.

The general symptoms of brain tumour are headache, generalised seizures, altered level of consciousness and diplopia. Most of the headaches associated with brain tumours are non-specific. Headaches usually arise due to traction on pain-sensitive structures such as dura and blood vessels. Headaches may be unilateral, in which case they may indicate the side of the lesion (but not its exact location). The headaches are often of moderate to severe intensity and can last for hours. Headaches which occur in early morning[2] and which improve within an hour of awakening and headaches immediately followed by vomiting[3] are more suggestive of brain tumours. Papilledema may be present in 25 per cent of brain tumours. Nausea and emesis may occur in brain tumours even without concomitant presence of headaches, and are presumably related to elevated intracranial pressure. The elevation of intracranial pressure can also result in excessive daytime sleepiness or lethargy. Diplopia is also a not uncommon complaint but is not of localising value. It is usually related to a sixth nerve paresis secondary to raised intracranial pressure (false localising sign). Generalised seizures may occur in about 20 per cent of patients and are related to irritation and compression of adjacent brain tissues.

Specific localising symptoms depend on tumour location and the neurological structures compressed. Table 9.38 summarises the symptoms of common tumours based on their location and likely histopathology.

Diagnosis When a brain tumour is suspected, an imaging study of the brain should be obtained as soon as possible. The choice of the imaging technique is based on availability and expense. Generally, an MRI scan is the imaging modality of choice for evaluating brain tumours. It is especially preferable for brainstem and posterior fossa tumours. The MRI scan is usually combined with a paramagnetic contrast agent (gadolinium-DTPA). A brain tumour appears as an area of altered signal intensity with surrounding edema and mass effect. Most malignant tumours enhance with contrast (because of an altered blood-brain barrier in the neovessels). A contrast-enhanced CT scan also reveals the enhancing mass lesion with surrounding edema; it is less expensive and remains an excellent diagnostic technique for supratentorial tumours.

Treatment General measures for treatment of patients with brain tumours include anticonvulsants for seizure and measures to decrease brain and peritumoral edema. For the latter purpose, low-dose dexamethasone may be used, provided a primary CNS lymphoma is not a possibility. In the latter case, the lympholytic effect of steroids can excerbate cerebral edema further.

Surgical excision is the treatment modality of choice for most brain tumours. Often benign tumours (such as meningioma, pilocytic astrocytomas, schwannomas) can be excised completely. Even for malignant tumours (such as glioblastoma multiforme) complete excision is a better option than biopsy or partial excision. After surgical excision, radiation therapy (usually fractionated external beam radiotherapy) is recommended for all malignant tumours and some benign ones; radiation

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[1] Similar to the mechanism of edema in stroke and head trauma. The other type of cerebral edema is cytotoxic edema, in which the intracellular water content is increased (as in hyponatremia), the blood-brain barrier remaining intact.

[2] It is believed that nocturnal hypoventilation results in elevated PCO_2 and this in turn results in increased cerebral blood volume and peritumoral edema.

[3] Migraine headaches are more prolonged and vomiting occurs after a while.

Table. 9.38 Clinico-pathologic correlation of primary nervous system tumours (based on location)

Tumour location	*Likely histopathology*	*Common clinical findings*
Cerebral hemispheres	glioblastoma multiforme, metastases, meningioma, astrocytoma, oligodendroglioma	headaches, seizures, motor paralysis, homonymous hemianopia (see 'lobe syndromes')
Optic nerve	astrocytoma	proptosis, monocular blindness, associated neurofibromatosis
Sellar and parasellar region	pituitary adenoma, craniopharyngioma, teratoma	**endocrine**: hypo/hyperpituitarism, amenorrhea galactorrhea, diabetes insipidus **neurologic**: bitemporal hemianopia, oculomotor palsies
Pineal	germinoma	**endocrine**: precocious puberty **neurologic**: hydrocephalus, paralysis of upward gaze
Third ventricle	choroid plexus papilloma	intermittent attacks of acute hydrocephalus, drop attacks
Cerebellum	medulloblastoma, astrocytoma, hemangioblastoma	ataxia, incoordination, nystagmus, early hydrocephalus
Cerebellopontine angle	acoustic neuroma, meningioma	unilateral tinnitus, deafness, vertigo, ipsilateral ataxia, fifth and seventh cranial nerve paresis
Brainstem	astrocytoma	multiple cranial nerve palsies with sensorimotor findings, ataxia, hydrocephalus
Spinal canal	neurilemmoma, meningioma, ependymoma	radicular pain, sensorimotor findings based on level of tumour, sphincter dysfunction

therapy has been shown to prolong survival in patients with glioblastomas, medulloblastomas, and ependymomas. Spinal irradiation is also required for medulloblastomas and ependymomas as these tumours often seed the meninges. Chemotherapy is a useful adjunct to surgery, especially in malignant astrocytomas; nitrosureas are most often used along with other anticancer drugs.

Prognosis Age, histologic grade, extent of tumour at the time of diagnosis and location are important prognostic factors. Generally, prognosis is better in young patients and those with low-grade tumours. For instance, a pilocytic astrocytoma is compatible with a normal lifespan whereas the median survival for glioblastoma is about one year. Other tumours have an intermediate median survival (astrocytoma: 5–10 years, anaplastic astrocytoma: 2–3 years).

KEY CONCEPTS

- *Secondaries* (metastases) are more common than *primary* tumours. Primary tumours have a bimodal age incidence, are more common in men than women (with the exception of meningiomas and schwannomas).
- A majority of tumours (60%) are gliomas (75% of which are malignant). There is an association with neurocutaneous syndromes.
- *Posterior fossa* tumours are more common in children (e.g. medulloblastoma) and present early with symptoms of raised intracranial tension. *Supratentorial* tumours are more common in adults.
- Symptoms of a brain tumour depend on its *location, size,* and *rate of growth.* Symptoms may be related to increased intracranial tension (headache, papilledema). Seizures occur in hemispheric tumours.
- Neurologic signs depend on location. *Sellar* and parasellar tumours cause visual field defects and endocrine manifestations. *Pinealomas* are associated with precocious puberty. *Brainstem gliomas* cause multiple cranial nerve palsies and long tract signs and variable degree of paresis of limbs. *Cerebellar tumour* present with ataxia and intention tremors. *Cerebellopontine angle* tumours cause decreased hearing, tinnitus, diminished corneal reflex, and facial paresis.
- CT scan or MRI are the investigations of choice.
- Treatment modalities vary depending on the tumour. Surgical excision is often feasible for meningiomas and low grade gliomas. Malignant gliomas are treated with a combination of surgery, radiation and chemotherapy. Chemotherapy is the treatment of choice for intracranial lymphomas. Medulloblastomas are treated with radiation. High dose radiation may also be required for complications like cord compression. Raised ICT can be managed with hyperventilation, corticosteroids, and mannitol.

9.16 Head injury

Any injury to the head is not a head injury. A patient who sustains an injury to the head must have an element of altered sensorium, however transient, to be included in the category of 'head injury' patients.

Pathophysiology and pathology The brain is protected by a very hard covering provided by the skull. The clinically different spectrum of lesions encountered following head injury arises from two main factors, that is, the differences in the skull characteristics and the differences in the viscoelastic properties between the skull and the brain on the one hand and the different parts of the brain on the other. At the extremes of ages the dura is firmly adherent to the inner table of the skull. Thus, the frequency of extradural hematomas is much lower in these groups.

Imagine a head-on collision between two cars. At the moment of impact the instinctive protective reflex of the driver is to swiftly turn the head and protect it with the hands. In this act acceleration is applied to the head. The bony hard skull turns swiftly but there is a time lag which is required for the brain to absorb this impact, get into motion and acquire the acceleration. This occurs as the brain is 'floating' on the cerebrospinal fluid within the bony skull. The brain is not a homogeneous structure. There is a difference in the tissue density between the different parts such as the cortex, subcortex, and basal ganglia. Consequently, these layers move with different accelerations and *momentarily* slide over each other resulting in disconnections between these layers.

There is a centripetal transmission of the force of impact. Consciousness is lost when the reticular activating system (RAS) at the level of brainstem is involved. The severity of coma is determined by the severity of impact forces transmitted.

Angular acceleration results in '*coup*' injuries. This occurs as the 'deformed' brain absorbing the forces of impact, rubs against the inner table of skull, or the falx.

On the other hand, a focal injury, (such as, a direct hit on the head by a hammer) results in a local injury at that site. As the skull absorbs the impact it deforms. If the impact is severe, it breaks resulting in a fracture which is often stellate. If the impact is more severe, there may be a tear in the underlying dura and the underlying brain. These forces result in *compound* head injuries. A fracture thus produced may at times involve the air sinuses: this is known as an internal compound injury.

Head injury produces a wide variety of lesions:

1. Concussion
2. Contusion hematomas
3. Intracranial hematomas : extradural, subdural or intracerebral.

Clinical features 1. Concussion: This refers to an immediate loss of consciousness with no demonstrable anatomical or pathological changes. This results from a transient electrophysiologic dysfunction of the RAS in the upper midbrain caused by rotation of the

cerebral hemispheres on a relatively fixed brainstem. CT and MRI are normal. Amnesia after concussion typically recovers after a few moments of unresponsiveness.

In a few patients there may be no loss of consciousness following the impact but there may be evidence of focal cerebral dysfunction, for example, focal weakness which recovers rapidly. These cases may be labelled as having suffered from 'focal concussion'.

2. Intracranial contusion hematomas: A contusion is a laceration of the brain associated with areas of hemorrhage.

3. Extradural hematomas (EDH): This refers to the collection of blood between the skull and the dura mater. The blood may be from the fracture site or due to the laceration of an artery such as the middle meningeal artery. EDH is an uncommon type of injury, accounting for 5 per cent of head injury cases. A lucid interval lasting from minutes to hours occurring prior to the onset of coma is said to be highly suggestive of extradural hematoma. This is a misconception as this type of head injury is distinctly uncommon.

4. Acute subdural hematoma (SDH): This refers to the collection of blood between the dura and the brain. There is no such entity as a 'pure' acute SDH, as there is always an underlying contusion. Upto a third of cases have a lucid interval before coma supervenes.

5. Chronic subdural hematoma: This condition is usually seen in elderly patients, usually weeks or months after a head injury. It should be suspected when there is a waxing and waning of sensorium. Raised intracranial pressure with headaches and papilledema may be the presenting features.

Of all patients in coma brought to the emergency following a head injury, 40–50 per cent will have an intracranial hematoma. There are three types of situations that may occur: 1) the patient may show progressive improvement in sensorium 2) the patient may show no improvement in sensorium since admission, but no deterioration either, and 3) the patient may show gradual or rapid deterioration.

It is estimated that 3–4 per cent of patients walking into the emergency room will eventually require surgical evacuation of an intracranial hematoma.

Management A patient who sustains severe head injury suffers not only one injury but three injuries. The primary injury to the brain occurs at the moment of impact:the first accident. The second accident occurs during the transfer of such a patient by inexperienced bystanders to the hospital. The third accident occurs while the patient waits unattended in the hospital for investigations. The second and third accidents occur primarily due to inattention to the airways and delay in the detection and management of shock. This results in secondary brain damage due to hypoxia, hypercarbia and impaired cerebral perfusion.

It is impossible to control raised intracranial tension without the restoration of the patency of airways, and normalisation of blood pressure. This should be done as soon as the patient is received in the casualty department.

The presence of shock should alert the surgeon to the possibility of severe chest or abdominal injury or major long bone injuries. Pelvic injuries with retroperitonial hematoma and cervical spine injury should be considered if no obvious cause of hypotension is found. Hypotonic intravenous fluids should be avoided as they tend to aggravate brain edema; fresh blood is preferred for the initial resuscitation.

The cases which should be investigated further are:

1. all patients who are brought in a comatose state, as the likelihood of an operable intracranial lesion is 40 per cent;
2. a patient who does not regain normal sensorium and continues to be disoriented during observation in the emergency;
3. a patient who rapidly deteriorates in sensorium. This is likely to occur within 48–72 hours after head injury due to brain edema or

Fig 9.44a Battle's sign
Battle's sign, a bruising over the mastoid area, is often seen in fractures of the basilar skull.

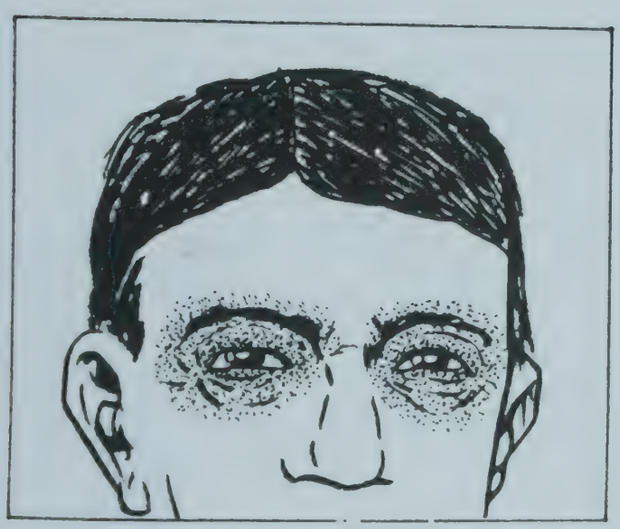


Fig 9.44b
Raccoon's eyes, a bilateral bruising of the periorbital area, is also associated with basilar skull fractures

following a convulsion. Such patients are likely to have operable lesions.

4. Patients with compound injuries with CSF leak from the wound site or with herniation of edematous brain from the wound site;

5. a patient complaining of persistent headaches;

6. patients with CSF rhinorrhea persisting beyond three weeks.

Plain radiographs of the skull are not very informative in the majority of cases but are still taken as a part of medicolegal formalities.

Computerised tomography of the head provides information in the majority of cases and is the investigation of choice. Its major advantage is that it allows the distinction between operable and non-operable cases.

Role of cerebral pharmacologic protectors
Mannitol and barbiturates have been found to have clinically demonstrable beneficial effects in severe head injury cases. Experience with barbiturates is restricted to a few centres in the world. Mannitol is routinely used in a dose of 7 ml/kg divided at 6–8 hour intervals. The clinical efficacy is best seen in the first week. Severe dehydration and electrolyte imbalances may occur and monitoring of serum osmolality and electrolytes should be done regularly.

Prognosis 1. Age: This is the single biologically important factor in determining the outcome following head injury. In one large study of severe head injury cases, 55 per cent of children had a good outcome at 1 year, compared to 21 per cent of adults.

2. Glasgow coma score: Eighty-five per cent of patients with a coma score of 3 or 4 will die within 24 hours. Scores above 11 indicate a 5–10% chance of dying. Scores, between 5 and 10 are associated with an intermediate prognosis.

3. Abnormal CT scan: Patients with an operable hematoma on CT have a better prognosis provided they are operated before developing clinical evidence of brain death.

4. Abnormal brainstem reflexes: These are a sensitive index of prognosis in cases of severe head injury. The oculocephalic reflex and the caloric test are most informative.

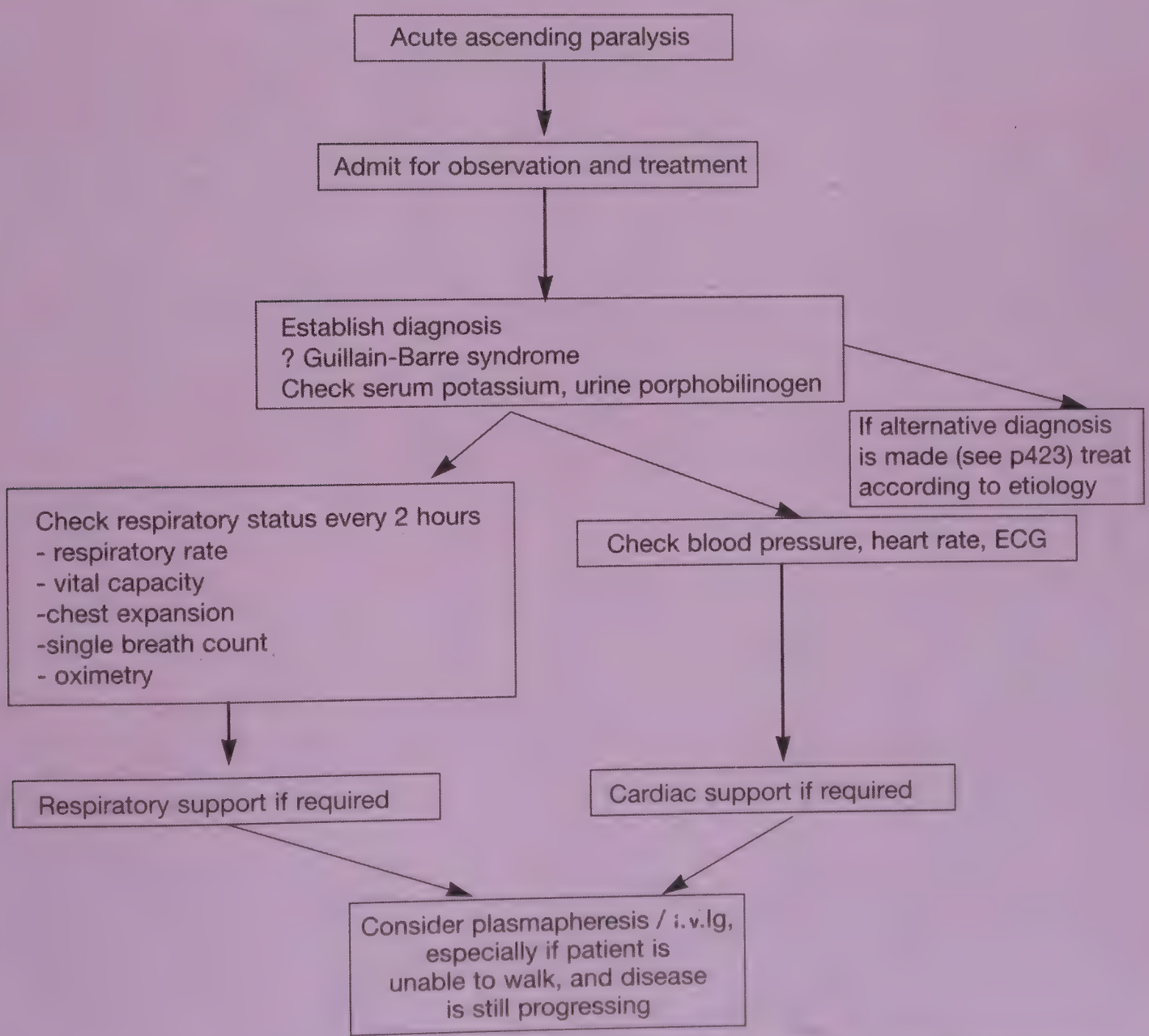
5. Evoked potentials are probably more accurate then clinical observations and intracranial pressure recordings. Somatosensory evoked responses are the most useful. Bilaterally absent cortical potentials are predictive of death or a vegetative state in 85–95 per cent of cases.

KEY CONCEPTS

- Damage results from direct penetration or due to rapid brain acceleration and deceleration (*coup* and *contrecoup*).
- Skull fractures can lacerate the meningeal arteries or large dural venous sinuses and result in *epidural* and *subdural* hematomas.
- A *concussion* is a momentary disruption of brain function following head injury which results in a brief loss of consciousness. *Contusions* and *lacerations* represent more severe degrees of head injury.
- A *subdural* hematoma can present as *acute* (altered sensorium with focal neurologic signs) or chronic (minor remote trauma, headaches and chronic behavioural changes).
- Management of a patient with head injury includes ensuring airway patency, ventilatory and circulatory support (if needed), obtaining an emergent CT scan to delineate potentially operable hematomas, control of intracranial pressure and neurosurgical evacuation of hematomas.

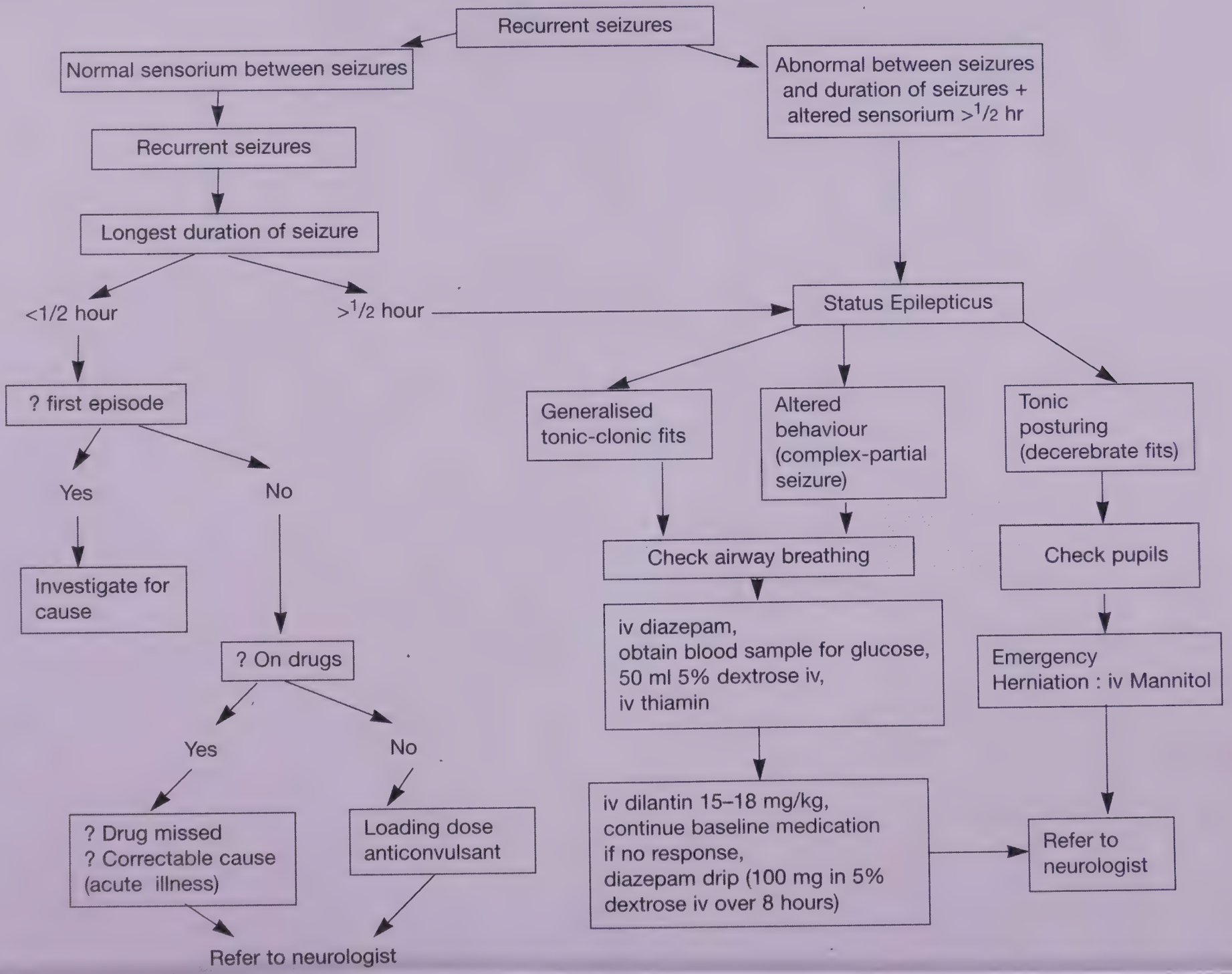
9.17 Neurologic emergencies*

1. Approach to a patient with acute ascending paralysis



* For other neurological emergencies (TIAs, stroke, coma, head injury, acute cord compression, myasthenic crisis) see relevant sections.

2. Management of recurrent seizures



10

Psychiatric Diseases

10.1 Approach to a patient with psychiatric disease

The practice of psychiatry requires a greater mastery of the *art* of medicine than the practice of any other branch. In approaching the patient we must take *conscious care* to be as patient, unprejudiced, non-judgemental and genuinely empathic as possible.

History Psychiatric history-taking takes *time.* It also requires talking separately to the patient, immediate family, close friends and teacher or employer, encouraging and specifically probing for sensitive or embarrassing details which may be relevant. Needless to say, the case-sheet should be confidential and accessible only to the treating team.

Onset and course The onset of illness is usually early in the major psychoses. Onset after the age of forty years should make one question the diagnosis. An underlying cause (so-called 'organic etiology') such as a medical or neurological illness is often responsible for 'psychiatric' symptoms in the elderly.

Precipitating causes should be looked for. These include the loss of a loved one, money or a job; the stress of marriage (specially for women who sometimes have to move to an alien household), childbirth and divorce; intake of any drug either illicit or prescriptional, and the stress of a physical illness.

A self-limiting course and normal functioning between psychotic episodes are in favour of a manic-depressive psychosis rather than schizophrenia.

Premorbid personality

This refers to the nature of the individual prior to the onset of the illness. Schizophrenic patients have often always been aloof, have few friends none of whom are close, and have problems in their marriage, work and social life (interpersonal inadequacy). Manic-depressive patients have often had marked mood swings (cyclothymic personality). Sociopaths usually have a history of theft, vandalism or truancy even prior to the age of 15 years.

Social background and family history In addition to looking for physical or sexual abuse as a child (often by an uncle, stepfather or member of the household) and any other etiological or precipitating factors, one should look for possible 'secondary gain' due to the symptoms. In a major psychosis there is usually no secondary gain due to the symptoms. In malingering there is usually an obvious 'pay- off' in the form of financial compensation, attention and kindness which are otherwise not available, or making someone feel guilty (for example, a parent whose child wants to marry a person he/she considers unsuitable). In 'hysteria' the gain may be less obvious but the total absence of a precipitating factor or secondary gain should make one seriously doubt the diagnosis.

Approach to a Patient with Acute Psychoses

Acute psychosis is a term indicating the development of symptoms of gross impairment in reality, usually over the course of days to weeks. Symptoms include delusions, hallucinations and ideas of reference. Other associated symptoms include anxiety, psychomotor agitation or retardation, rapid mood changes and poor judgement.

Etiology Acute psychosis is not a diagnostic entity; it is a clinical syndrome encompassing several etiologic possibilities that are listed in Table 10.1.

Clinical approach A careful elicitation of history is essential to confirm the presence of psychotic behaviour and to establish a cause. It may be necessary to obtain a proper history from a family member or a friend. A previous history of a similar episode must be sought along with details of any hospitalisation. The use of psychotropic medication or drug abuse must be determined discretely. Physical examination is guided by a proper general physical examination, a detailed examination of the neurologic system and of the mental state. The grooming and appearance of the patient must be noted. The speech is noted for its rate (rapid, slow or halting), amount (grandiosity or paucity) and tone ('sing-song' or slurred). The thought process is assessed for its flow, logic and associations. Loose associations are indicated by the shifting of ideas from one to the other without a logical connection. Tangentiality (that is, wandering off a subject but speaking related words), flight of ideas (quick change of ideas) and rapid speech often indicate a psychosis. The mood (the internal emotional state) and affect (the outward expression of the internal emotional state) of the patient are noted. Speaking to the patient may reveal the presence of delusions or hallucinations. Delusions are false beliefs that are outside the patient's culture. Delusions of reference involve the belief that a particular object or person has special powers in relation to the patient. Hallucinations are false perceptions of a sensory stimulus when, in fact, there is none. They may involve any of the sensory modalities. Auditory hallucinations are seen in psychoses. Visual psychoses are common in toxic and drug-induced states. Gustatory (related to taste) and olfactory hallucinations may indicate temporal lobe disorders. Tactile hallucinations are seen in drug withdrawal states or in cocaine abuse. Other disorders must be

Table 10.1 Causes of acute psychotic behaviour

Major psychiatric diseases	*Medical conditions*	*Toxic or drug-induced*
Mania	Metabolic diseases	Amphetamines
	-uremia	Hallucinogens
Depression	-dyselectrolytemia	-LSD
	-hypoglycemia	-Datura poisoning
Exacerbation of	Endocrine diseases	Volatile hydrocarbons
	-hypothyroidism	-gasoline
schizophrenia	-hyperthyroidism	-paint
	-hypercalcemia	-toluene
	Organic brain syndrome	Tricyclic antidepressants
	-encephalitis, meningitis	Antiparkinsonian drugs
	-Wernicke-Korsakoff psychosis	-L-dopa
	-subdural hematoma	

considered in the differential diagnosis. Patients with drug-induced extrapyramidal reaction may appear agitated and psychotic but a history of drug intake serves to establish a diagnosis. Signs of hypothyroidism or thyrotoxicosis must be sought carefully as occasionally both these disorders can present as acute psychoses. The presence of an oculomotor palsy or ataxia in a confused patient may indicate a Wernicke-Korsakoff psychosis.

Investigations A complete blood count and electrolyte estimation is useful in the investigation of an acutely psychotic patient. Blood glucose and urea estimations are helpful in establishing a metabolic cause of psychotic behaviour. Infections can cause an encephalopathy characterised predominantly by psychotic features such as enteric encephalopathy due to Salmonella typhi. Blood cultures may be obtained if an infection is suspected. A sample of blood may be preserved for toxicological purposes if facilities for such estimations are present. A thyroid hormone profile may be ordered if facilities for estimation are available.

Management Hospitalisation is usually required in the acutely psychotic patient for the purposes of stabilisation, diagnostic evaluation and for initiating specific treatment. Benzodiazepines (diazepam 5–10 mg i.v. or lorazepam 0.5–1.0 mg i.m.) provide adequate control for the agitated psychotic patients. Neuroleptics (haloperidol 5–10 mg i.m.) may be used for psychoses with prominent thought disturbances. Therapy for psychotic behaviour secondary to drug abuse is supportive and symptomatic. Patients with anticholinergic intoxication (tricyclic antidepressants) respond to physostigmine. Treatment of Wernicke's encephalopathy requires the administration of thiamine (100–200 mg i.m. or i.v.).

Approach to a Patient with a Depressive Syndrome

Depression is a disturbance of mood characterised by sadness that is intense and continues beyond the expected impact of a stressful life event. The various causes of a depressive syndrome have been listed in Table 10.2.

Clinical approach A careful history is essential to substantiate the presence of depression and to search for a treatable cause. Sadness is an important part of life and must be distinguished from depression, which is prolonged and not adaptive. Transient depressive periods are common and may be related to some events such as a death anniversary or menstrual periods. Bereavement is the normal reaction to the death of a loved one and lasts from 2–6 months. A careful history of drug intake is required in any depressed patient. Several categories of antihypertensive agents can cause depression by their modulation of the central nervous system amines. Withdrawal of corticosteroids can cause depression especially if the withdrawal is abrupt. Chronic use of depressive substances such as alcohol or barbiturates can mimic a depressive state. The presence of any chronic debilitating cardiopulmonary disease or a neoplasm can set the stage for a depressive syndrome. Endocrine assessment for the presence of hypercortisolism is important as it is frequently accompanied by depression.[1] The presence of central obesity, cutaneous striae, hirsutism and acne are valuable clinical clues for the presence of Cushing syndrome. Clinical assessment of thyroid function is important as both hyperthyroidism and hypothyroidism can cause a depressive illness. The presence of goitre, heat or cold intolerance, bowel disturbances, peripheral signs of altered thyroid function (tremors, pretibial edema, 'hung-up' tendon reflexes) must be sought. Depression may be an important feature of the acquired immunodeficiency syndrome (AIDS); it may either be due to cerebral involvement or occur as a reaction to the disease itself. A careful neurologic examination is

[1] Exogenous corticosteroids often cause euphoria whereas endogenous cortisol excess causes depression.

important to exclude any organic neurological cause of depression (Table 10.2). Subjects with dementia share several features with those with a primary mood disturbance and lack of concentration, memory lapses and poor performance on mental status exams are common to both. Usually subjects with dementia are not self-reproachful, have a greater loss of recent memory, as compared to equal loss of recent and remote memory in the depressed subject, and do not have a past history of similar episodes. When a distinction is difficult, a depressive illness may be provisionally diagnosed and a trial of antidepressants initiated due to the better prognosis of depression. Subjects with severe depression may have associated features of hallucinations, which raises the possibility of schizophrenia; indeed the history and, on occasion, the temporal course alone may help differentiate the two illnesses. A history of depression related to a specific season, usually winter, suggests a seasonal affect disorder. The specific features of a primary mood disorder include the presence of sadness of affect, anhedonia (lack of interest in any activity which gives pleasure), psychomotor retardation, early morning awakening and feelings of worthlessness in the absence of any of the above systemic illnesses. Differentiation of depression from related disorders like dysthymia or cyclothymia is detailed in a later section.

Investigations The dexamethasone suppression test and the sleep EEG latency findings are helpful in the diagnosis of a primary mood disorder. These tests are discussed in detail in the section on mood disorders. Thyroid hormone tests may be obtained if there is a high index of suspicion of a thyroid disorder.

Treatment Treatment of the secondary cause of depression can often alleviate the symptoms promptly. The treatment of primary mood disorders is discussed in a separate section.

Table 10.2 Causes of depressive syndromes

1. Psychiatric disease
   - primary mood disorders
   - schizophrenia
   - somatisation disorders
2. Drugs
   - steroids
   - phenothiazines
   - reserpine
   - β-blockers
   - cimetidine
   - central α agonists (M-dopa, clonidine)
   - Vinca alkaloids
3. Infections
   - tertiary syphilis (general paresis)
   - AIDS
4. Endocrine disease
   - hypothyroidism
   - hyperthyroidism
   - Cushing's disease
   - Addison's disease
5. Neurologic disorder
   - dementia
   - multiple sclerosis
   - Parkinson's disease
   - stroke
6. Cancers
7. Chronic debilitating conditions: CHF, fractures

KEY CONCEPTS

Delirium

- ➢ This refers to an acute widespread brain dysfunction which may be due to neurologic, systemic or psychiatric causes.
- ➢ It is important to distinguish *functional* from *organic* causes. The presence of fever, drug use, systemic illness, focal neurologic signs, an acute onset in a patient without prior history of psychiatric illness and a rapidly fluctuating level of consciousness suggest an organic etiology. If mental state examination reveals defects in orientation, recent memory or performance of intellectual tasks, a non-organic cause is likely.
- ➢ Important investigations include routine hematological tests (including peripheral smear for parasites) and biochemical screening (electrolytes, renal and liver functions), chest X-ray and arterial blood gas analyses. Consider CSF examination if meningoencephalitic illness is likely.
- ➢ The treatment depends on the underlying etiology. Minor or major tranquillisers may be required for controlling the patient.

Depression

- ➢ Depression is very often part of a medical problem; organic cause should before labelling as primary mood disorder.
- ➢ HIstory and physical examination be excluded and so vital in establishing the diagnosis: long-standing history of a debilitating illness (cancer, CHF, neurologic disease), chronic infections (HIV), drug or substance abuse, and endocrinopathy (thyroid or adrenal hypo/ hyperfunction may be associated with mood changes).
- ➢ The treatment is dependent on etiology.

10.2 Anxiety disorders

This group of disorders includes several entities all characterised by anxiety as a central feature. Generalised anxiety disorders, panic disorders, obsessive compulsive disorders and phobias are included in this category.

Generalised Anxiety Disorder

A *generalised anxiety disorder* is present if a subject experiences unrealistic worry about two or more life circumstances for a period of six months or more along with at least six symptoms of anxiety (see below).

Clinical features The symptoms of anxiety are chronic and include cardiac (tachycardia, palpitations, increased blood pressure), gastrointestinal (increased acidity, difficulty in swallowing), neurologic (tremors, muscle tension, sleep disturbances, difficulty in concentration, exaggerated startle) and autonomic disturbances (flushes of chill, frequent urination, dry mouth, increased sweating). The anxiety tends to be chronic although a third of the patients usually recover. Men generally have a better prognosis than women. The disorder can render the subject chronically uncomfortable in daily activities.

Treatment The first step in the management of these subjects is the identification of any stressors. The stressful situations can either be removed or the patient counselled as to how to cope with the situation.

The two main classes of drugs that are effective in the treatment of generalised anxiety disorders are 5-hydrotryptamine receptor agonists (buspirone) and benzodiazepines (Table 10.3). Buspirone has the disadvantage of a delayed onset of action and a need for continuous medication but unlike benzodiazepines, it is free from the side effects of sedation such as alterations in memory and the potential for dependence and withdrawal effects.

Panic Disorder

This disorder is characterised by recurrent, short-lived episodes of sudden apprehension or fear usually accompanied by an automatic arousal reaction. These episodes are called panic attacks and the diagnostic criteria require the occurrence of at least four such attacks over a four-week period.

Clinical features Panic disorders characteristically occur in young adults; women are affected twice as often as men. There is a heightened vulnerability in the premenstrual period in women. Somatic symptoms accompany the panic attacks and include cardiorespiratory (shortness of breath, palpitations, sharp precordial pain, choking), neurologic (tremors, sweating, dizziness, paresthesias) and gastrointestinal symptoms (nausea, diarrhea) of an alarm response. Attacks may last from a few minutes to an hour. Hyperthyroidism, pheochromocytoma, atrial tachycardia, hypoglycemia and the carcinoid tumour are other diagnostic

Table 10.3 Drugs for treatment of anxiety disorders

Class	*Usual oral dose (mg)*	*Maximum daily dose (mg)*	*Comments*
A. Benzodiazepines			
(i) Intermediate acting (8–16 hrs)			
Alprazolam	0.5	4	for anxiety and sleep disorders
Lorazepam	2–4	10	
Oxazepam	10–30	60	
(ii) Long acting (>20 hrs)			
Diazepam	5–15	30	
Clonazepam	1–2	10	
Chlordiozepoxide	10–20	40	
(iii) Ultra short acting (3–5hrs)			
Triazolam	0.125	0.25	
B. $5HT_{1A}$ agonists			
Busiprone	10–30	60	
C. 5HT* reuptake inhibitors			
Fluoxetine	20–60	80	for panic disorders
D. Miscellaneous			
Clomipramine	25–200	250	for panic disorders
Hydroxyzine	50	100	for sleep disorders

*5HT = 5-hydroxytryptamine

entities that may have a presentation like a panic attack and must be excluded as diagnostic possibilities.

Treatment Antidepressants are the drugs of choice for the treatment of panic disorders. Fluoxetine and tricylic antidepressants are effective. Alprazolam (0.5–5 mg/day) and clonazepam (0.5–4mg/day) are effective but benzodiazepines are generally avoided due to significant dependency problems.

Obsessive Compulsive Disorder

The term obsession refers to a persistent recurrent idea, thought, feeling or impulse.

A compulsion is a repetitive, stereotyped action or behaviour. An obsessive-compulsive

disorder is characterised by the presence of obsession (the thought component) that leads to compulsion (the action component) that the patient recognises as morbid and resists often, in vain.

Clinical features Obsessive-compulsive disorders are uncommon, occur equally in both sexes and usually have an onset in adolescence. There is a higher incidence in the more educated classes of society. The patient usually repeats a certain behaviour as an expression of anxiety. Unlike phobias where the anxiety is due to external stimuli, the anxiety arises in response to 'internally' derived thoughts. The patient may repeatedly wash hands to ensure they are clean, close and lock doors repeatedly to ensure safety, or constantly rearrange the house to ensure orderliness. The disorder tends to be chronic, often with remissions and relapses. The behaviour may significantly impair social and occupational function.

Treatment Chlorimipramine and high dose fluoxetine have been used to treat obsessive-compulsive disorders. Behavioural therapies have an important adjunctive role.

Phobic Neurosis

Phobic disorders are characterised by the presence of a persistent irrational fear of objects, places and situations that are not inherently a source of danger or anxiety.

Clinical features The irrational fear (phobia) compels the patient to avoid the object or situation that arouses it. Anxiety is a prominent feature but unlike the 'floating' anxiety of generalised anxiety disorders, the anxiety is linked to specific environmental objects. The disorder usually manifests in the third decade of life with a female preponderance.

Three types of phobias have been identified. Simple phobias are quite common; the patient fears animals, the dark or heights. These phobias often develop in childhood and usually no disability develops if the object or situation is avoided. Agoraphobia is a fear of open public places or crowds. It is the commonest of the phobic disorders, affects women more often and tends to be chronic. These patients often restrict their normal activities and confine themselves to their homes. Social phobias arise from a fear that one might embarrass or humiliate oneself in public. These phobias are common among adolescents and involve specific functions such as eating in a public place or speaking in public.

Treatment Phobic disorders may never be completely cured. The aim of therapy is to help the patient function adequately and effectively. Behavioural therapy uses systemic desensitisation techniques; the patient is made to confront the stimulus while using relaxation techniques. Minor tranquillisers (benzodiazepines, buspirone) are helpful in reducing anticipatory anxiety.

KEY CONCEPTS

- ➢ *Panic attacks* occur as episodes of palpitation, shortness of breath, choking sensation, dizziness and autonomic arousal; four attacks within four weeks are required for making a diagnosis.
  - It must be distinguished from *generalised anxiety disorder* in which symptoms occur almost everyday without discrete episodes.
  - Antidepressants are preferred to high potency benzodiazepines (risk of dependence).
- ➢ *Phobia* is an irrational fear of objects, places or situations.
- ➢ *Obsessions* are recurrent ideas and impulses. *Compulsions* are repetitive stereotyped actions. Chlorimipramine may be helpful in obsessive-compulsive disorders.

10.3 Major mood disorders

MAJOR DEPRESSIVE EPISODE

This diagnosis requires the presence of at least five of a constellation of nine depressive symptoms lasting for at least two weeks and one of the symptoms should be a depressed mood or loss of interest.[1]

1. depressed mood most of the day, nearly every day.
2. anhedonia — marked dimunition of interest in all activities
3. significant decrease in appetite (or increase) and loss of weight (or increase) >5% of body weight in one month
4. insomnia or hypersomnia
5. psychomotor agitation or retardation
6. fatigue or loss of energy
7. feelings of worthlessness
8. indecisiveness or inability to concentrate
9. recurrent thoughts of death or suicide

Clinical features and categorisation The chronically depressed patient often enters the physician's office walking slowly with drooping shoulders and an omega sign (facial wrinklings over the bridge of the nose like an Ω). There may be changes visible in the clothing, grooming and personal hygiene. Further steps in evaluation include ruling out a secondary mood disorder, recognising atypical features, psychotic features, melancholic or dysthymic features, associated mania/hypomania and seasonal features. Such an approach has important therapeutic implications.

Atypical depressions are characterised by a tendency to gain weight and hypersomnia rather than weight loss and insomnia, and a feeling of rejection everywhere. A diagnosis of major depression with psychotic features should be made when the subject has significant psychotic aspects to his depression, that is, the presence of delusions or hallucinations typically involving the themes of guilt, death or nihilism. Seasonal affective disorders are characterised by recurrent episodes of depression in the autumn and winter months with symptom-free periods in spring and summer.

Melancholic depression is said to be present whenever five of the following nine features are present:

1. loss of interest in all activities
2. lack of reactivity to usually pleasurable stimuli
3. worsening of symptoms in the morning
4. early morning awakening (two hours before the usual time)
5. psychomotor retardation or agitation
6. significant anorexia and weight loss
7. no previous personality disturbance
8. one or more previous depressive episodes (followed by recovery)
9. a good response to antidepressant management

[1] As defined by the 'Diagnostic and Statistical Manual of Mental Disorders' of the American Psychiatric Association

A history of mania or hypomania is important for a diagnosis of bipolar disorder.[1] *Mania* is suggested by the presence of grandiosity, distractability, irritability, decreased need for sleep, hypersexuality and altered judgement.

Dysthymia is said to be present when the patient has depression symptoms but there are also marked disturbances in personality.

Cyclothymia is characterised by both elevated and depressive periods of a lesser degree of severity, lasting typically a few days and follows an intermittent irregular course. It is a precursor of bipolar disorders.

The distinction of bipolar from unipolar disorders is clinically helpful. Unipolar disorders occur in older individuals (>25 years of age), episodes last for 6 to 9 months with a residual chronicity in 20 per cent of cases. Bipolar disorders have a younger age of onset, a shorter duration of episodes (3 to 6 months) and a shorter interval between two episodes. About 20 per cent of patients with an initial unipolar onset of disease switch to a bipolar form, almost invariably within a decade of the onset of the initial disease.

Diagnostic tests The diagnosis of a major affective disorder is based on clinical grounds. Three laboratory tests have been used as adjuncts. The TRH stimulation test assesses the change in plasma TSH levels after an intravenous injection of 500 μg of thyrotropin releasing hormone. A blunted response (defined as an increase of TSH <5 μU/mL) is seen in primary mood disorders and an exaggerated response (>20 μU/ml increase in TSH levels) is seen in some patients with a bipolar disorder. Failure to suppress serum cortisol levels after an oral intake of 1 mg dexamethasone (Dexamethasone suppression test) is characterstic of major depression but is also seen in pregnancy, Cushing's disease, uncontrolled diabetes mellitus and alcohol withdrawal states.

The REM latency refers to the time between the onset of sleep and the first rapid eye movement (REM) stage noted on a sleep EEG and has a mean duration of 90 minutes in normal persons. A shortening of the REM latency is typical of major depression. It should be kept in mind that these tests are used for screening purposes and cannot substitute clinical judgement.

Treatment is listed in Table 10.4.

Depression

Three classes of drugs are available to treat depressive episodes. The tricyclic antidepressants have an effect on the central and autonomic nervous system by means of the presynaptic blockade of norepinephrine or serotonin uptake. Their side effects include anticholinergic symptoms (dry mouth, blurred vision, constipation and urinary retention), alpha adrenergic blockade-related symptoms (orthostatic hypotension) and their quinidine-like effects (risk of conduction disturbances). The newer class of selective serotonin reuptake inhibitors do not have anticholinergic properties. The initial choice of an antidepressant may depend on the target symptoms. Nortriptyline may be better in subjects with an agitated presentation due to its sedative effects whereas fluoxetine or desipramine may be favoured in the subject with psychomotor retardation. The tricyclic antidepressants have the advantage of a greater clinical experience in their usage. It is generally advisable to start at the lowest dose marketed and to increase the dose gradually.

When anxiety is an important feature, a benzodiazepine may be added. Alprazolam, a benzodiazepine with a tricyclic ring structure, may be effective as monotherapy. When phobic symptoms are prominent, the MAO inhibitor phenelzine is very effective. Fluoxetine or clomipramine are the drugs of choice in patients with pronounced obsessional features. Tranylcypromine and

[1] 'Unipolar' disorder refers to recurrent episodes of major depression.

bupropion are more effective in seasonal affective disorders[1]. Electroconvulsive therapy (ECT) may be required for persistent suicidal ideation.

Manic Episodes

Lithium carbonate is the drug of choice in subjects with mania. It is started at a dose of 300 mg twice daily and increased over a 10-day period until serum levels of 0.8–1.2 mEq/L are achieved. Since lithium has a 4–7 day latency period, an antipsychotic agent such as haloperidol may be required to control the patient acutely. Some patients who have rapid cycling disorders (that is, increased frequency of mood cycles of shorter duration, usually less than 4 episodes per year), respond to carbamazepine or sodium valproate and thyroid hormone supplements (in the presence of borderline hypothyroidism).

Therapy for an isolated manic episode should continue for at least six months. If two or more classic bipolar episodes occur over a three year period, maintenance lithium (300 mg tid) must be instituted. Since lithium therapy is associated with a risk of Ebstein's anomaly in the first trimester of pregnancy, ECT may be used as an alternative for the treatment of the pregnant subject with mania.

[1] Seasonal affective disorders are disturbances in mood (usually depression) that occur typically with a change in season (usually in winter).

Table 10.4 Treatment of mood disorders

Class	*Usual daily dose (mg)*	*Maximum daily dose (mg)*	*Side effects*			
A. Drugs for treating depression						
i) Tricyclics			Anticholinergic	Orthostatic hypotension	Sedation	Effect on conduction system
Amitriptyline	150–250	300	+++	+++	+++	++
Nortriptyline	75–150	200	+	+	++	++
Imipramine	100–200	300	++	+++	++	++
Triimipramine	75–200	200	+	++	++	++
Clomipramine	100	250	++	++	++	++
Doxepin	25–150	300	++	+++	+++	++
ii) Heterocyclics (selective serotonin reuptake inhibitors)						
Fluoxetine	20	80	0	0	+	0
Trazodone	150–300	400	0	+++	+++	0
Bupropion*	300–450	450	+	+	0	0
iii) Monoamine oxidase inhibitors						
Tranylcypromine	10–30	50	orthostatic hypotension, hypertension with ingestion of tyramine rich food			
Phenelzine	45–60	90				
B. Drugs for treating manic episodes						
i) Mood stabilisers						
Lithium carbonate	900–2400	2400	tremors, polyuria, polydipsia			
Sodium valproate	500–1000	1500	gastrointestinal, hepatotoxicity			
Carbamazepine	400–1200	1600	sleepiness, ataxia, neutropenia			
ii) Anti-agitation agents						
Clonazepam	2–8	10	sedation, ataxia			
Lorazepam	2–4	6	sedation, ataxia			
iii) Antipsychotics						
Haloperidol	5–15	80	dyskinesias, akathisia, tremors, stiffness			

* Bupropion exerts its effects through the dopaminergic neurotransmitter system

KEY CONCEPTS

- Depression is a major disorder of *affect* which may be *unipolar* (depression alone) or *bipolar* (having depression and elated or excited periods [*mania*], a younger age of onset and shorter duration of episodes).
- *Depressive* episodes are characterised by sadness, crying spells, feeling of hopelessness, sleep disturbances, psychomotor retardation, suicidal tendencies and delusions (for example, of reference or worthlessness)
- *Manic* episodes feature psychomotor acceleration, racing thoughts, delusions (for example, of wealth), sleep disturbances and impulsive involvement in activities without recognising social dangers.
- Major depression is often treated intially with *selective serotonin reuptake inhibitors* (such as fluoxetine). Non-responders may be switched to tricyclic antidepressants. Refractory patients may require a trial of MAO inhibitors or ECT.
- For bipolar disorders, *lithium carbonate* is effective for treating acute manic episodes and for prophylaxis. Valproate and carbamazepine are alternative prophylactic agents.

10.4 Schizophrenic disorders

Schizophrenic disorders are a group of mental disorders characterised by psychotic symptoms involving disturbances in thought, perception, emotion and behaviour. Certain specific criteria have been laid out for these disorders, which include:

1. certain psychotic symptoms, delusions, hallucinations and thought disorders;
2. symptoms of disease for at least six months;
3. tendency to an age of onset before 45 years;
4. deterioration from a previous level of functioning; and
5. symptoms not due to either mood (affective) disorders or organic mental disease or mental retardation.

When the duration of symptoms is less than six months but other criteria are satisfied, the term *schizophreniform* disorder is used. If the psychotic symptoms are very brief (<2 weeks), the term *brief reactive psychoses* is preferable.

Epidemiology Schizophrenia becomes commonly manifest in late adolescence and early adult life. There is a higher prevalence in the lower socioeconomic classes, presumably related to stresses and social disorganisation; it may also reflect the drift of susceptible subjects to the lower social strata.

Classification and clinical features Five subtypes are described that vary significantly in their manifestations. *Catatonic schizophrenia* is characterised by prominent motor disturbances. Catatonia is a state of quantitative and qualitative alteration in motor activities. Catatonic stupor is a state of motor inactivity in which the subject may be immobile for weeks. Catatonic excitement is an emergency in which the patient is excessively active, often violent. Catatonic posturing is the assumption of strange postures for prolonged times. Catatonia must be differentiated from more common motor disorders. *Akathisia* is associated with motor agitation, which is usually a consequence of an intake of phenothiazine drugs. *Bradykinesia* is a condition in which there is a difficulty in initiating motor activity and is seen in Parkinson's disease. *Tardive dyskinesias* are unusual facial expressions associated with generalised choreoathetotic movements which are usually due to an intake of neuroleptic medication. The patient with catatonic schizophrenia also often shows bizarre stereotyped mannerisms, such as grimacing. There may be evidence of *perseveration,* the involuntary repetition of tasks, for instance repeating the answer to a question without stopping. *Paranoid schizophrenia* is characterised by persecutory or grandiose delusional thoughts and jealousy. It may not interfere with social functioning if the subject does not act on the delusions. This type develops later in life and tends to be stable over time. *Disorganised schizophrenia* (also called hebephrenia) is characterised by a silliness and incongruity of affect and extreme social withdrawal. Speech is often incoherent and chaotic. The term undifferentiated schizophrenia is used when the prominent psychotic symptoms cannot be classified under one of the above subtypes.

A diagnosis of residual schizophrenia is made when there is clinical evidence of illness but without prominent psychotic symptoms, and a previous history of at least one episode of schizophrenia with psychotic symptoms.

The disturbances of formal thought, thought content, perception, affect and movement that charcterise schizophrenia are listed in Table 10.5. Schizophrenic disorders must be distinguished from paranoid disorders. Paranoid states are characterised by persistent delusions without hallucinations and with a normal affect and social behaviour. While the delusions in schizophrenia are scattered, illogical, haphazard and have no relation to reality or real events, the delusions in paranoid states are systematised and usually based on a misinterpretation of reality.

Treatment The treatment of the schizophrenic patient consists of instituting antipsychotic drug medication, social support and gradual rehabilitation under the care of a skilled counsellor. Table 10.6 lists the commonly used antipsychotic drugs. All antipsychotic drugs except clozapine act by blocking the post-synaptic dopamine (D2) receptors and are equally effective. The choice of the agent may depend on the phase of the illness. In the acutely agitated patient, a high potency agent such as parenteral haloperidol (5 mg i.m.) may be used. Once the acute phase of agitation is controlled, treatment moves towards drug treatment of the fundamental deficits. Positive symptoms such as thought disorders, sleep alterations and hallucinations

Table 10.5 Disturbances in schizophrenia

Category	*Definition*
A. Formal thought	structure of thought as displayed by verbal communication
loosening of association	connection among ideas is obscure
neologism	new words created
verbigeration	persistent repetition of words or phrases
word salad	complete lack of language
lack of abstract thought	inability to understand
B. Thought content	
delusions	false beliefs
–of persecution	–that others are trying to harm them
–of grandeur	–they feel themselves to be very important
–of reference	–that random events (people, radio, TV) are harming them
–of nihilism	–imagined loss of world and self
C. Perceptual disorders	varying interpreration of sensory experiences
hallucinations	sensory experiences without environmental stimuli
–auditory	–complex voices
–command	–auditory command to do something
–visual	–visit from aliens
illusions	misidentification of environmental stimuli
–deja vu	–unfamiliar situation feels familiar
–jamais vu	–familiar situations feel unfamiliar
D. Affect	mood and emotion
blunted	–reduction of range and extent of feelings
inappropriate	–mismatch of thought and expression; laugh when someone is hurt
E. Movement	
catatonia	quantitative and qualitative change in movements (see text)

respond better than negative symptoms like amotivation, anhedonia and diminished insight and judgement. Clozapine may reduce the negative symptoms. The initial dose of the antipsychotic drug is slowly increased till a maximum clinical effect is achieved. This may take upto six weeks.

Once the accurate psychotic phase is controlled, the antipsychotic medication is continued at the maintenance dose that is approximately 20–30 per cent of the dosage required during the acute phase. The maintenance phase should be continued for three to six months and then slowly tapered over a trial period. Medication may have to be reinstituted during periods of stress.

Table 10.6 Antipsychotic drugs

Class	*Usual daily dose (mg)*	*Maximum daily dose (mg)*	*Side effects*	
			Extrapyramidal	*Postural hypotension*
i) Phenothiazines				
Chorpromazine	100–400	1000	++	++
Thioridazine	200–400	600	++	++
Trifluoperazine	5–15	60	++	++
Fluphenazine	2–10	60	+++	+
ii) Thioxanthenes				
Thiothixene	5–10	50	++	++
iii) Butyrophenones				
Haloperiodol	2–5	80	+++	+
iv) Dibenzoxazepine				
Loxapine	20–60	200	++	
Clozapine	300–450	900	0	+++
v) Dihydroindolones				
Molindone	30–100	225	++	+

* Fluphenazine is available as a long acting depot preparation, Fluphenazine decanoate or enanthate, 12.5–50 mg i.m. every 1–3 weeks.
* Haloperidol is available as a depot preparation, haloperidol decanoate 25–150 mg i.m. every 1–4 weeks.
* + mild, ++ Moderate, +++ severe.

KEY CONCEPTS

Schizophrenia

- This is an illness with psychotic disturbances of *thought, perception, feeling* and *behaviour.* High concordance rate in monozygotic twins suggests genetic predisposition.
- The onset is usually before 45 years of age. The course is typically punctuated by multiple relapses with incomplete recovery in between. Clinical features include delusions, blunt and inappropriate affect, impairment in grooming and hygiene, catatonic behaviour, deterioration from prior functional level, social isolation, prominent auditory hallucinations, and thought disturbances (loose associations, thought block and broadcasting).
- The diagnosis should be considered if symptoms persist for more than six months.
- The treatment consists of *neuroleptics* (for at least one year, with dose adjusted to minimise dyskinesia), social support and rehabilitation.

10.5 Somatoform disorders

This group of disorders includes symptoms and signs that are not under voluntary control and the affected patient is unaware of possible gains derived from those symptoms. There is no other organic disease that can explain these symptoms and signs. The group includes somatisation, conversion disorders and hypochondriasis.

Somatoform disorders must be distinguished from factitious disorders and malingering. In factitious disorders (Munchausen syndrome), the patients have voluntary control over signs and symptoms that have no organic basis. However, though the behaviour is deliberate, the motive for the behaviour is subconscious. Malingering is the voluntary faking of symptoms or signs of an illness with a conscious motive such as monetary, legal or other benefits.

Somatisation Disorder (Briquet Syndrome)

A somatisation disorder is likely to be present when multiple symptoms and signs that suggest a physical illness exist without any verifiable disease or pathophysiologic condition to account for them.

Clinical features The disorder begins in adolescence or early adulthood and predominantly affects women. A central feature is the presence of recurrent, multiple somatic complaints. The complaints are most often referable to the gastrointestinal tract and include abdominal pain, nausea and vomiting. Weakness, paresthesiae, headaches, dizziness, chest pain and palpitations are other frequent symptoms. Patients have frequently undergone repeated medical evaluations and may be quite knowledgeable about medical tests and terms. Anxiety and depression are common accompaniments of this disorder. The predominance, persistence and multiplicity of complaints helps differentiate these patients from those with anxiety disorders.

Treatment Treatment consists of acknowledging the patient's complaints and providing supportive sympathetic care to help the person live with the complaints.

Conversion Disorder (Hysterical Neurosis)

A conversion disorder involves the resolution of a psychological conflict by the unconscious conversion into a loss of a specific physical function.

Clinical features The disorder has an onset in adolescence and early adulthood. Although it is more common in women, it is also seen in men. Virtually any organ disease symptom can be simulated in a conversion reaction. Neurological symptoms such as weakness or paralysis of a limb are common. Other symptoms include blindness, seizures and aphonia. The patient has two gains arising from the conversion reaction. The primary gain is keeping away unpleasant mental contents from the consciousness, for example, loss of vision keeps the patient from seeing a situation. The secondary gain is the avoidance of unpleasant duties because

of symptoms. Hysterical deficits have to be differentiated from organic neurologic disease. Hysterical motor deficits often have a pattern that corresponds to the body image of the patient. Thus a 'glove and stocking' distribution, a non-dermatomal pattern or a distribution extending from head to toe exactly along the midline are common. In the patient with hysterical hemiplegia, the leg is dragged along without the usual circumduction movement seen in neurologic disease.

On muscle power testing, the patient displays great efforts to evoke a movement. There is usually an initial strong contraction that suddenly gives way when the examiner imposes a resistance. Hysterical blindness can be differentiated from organic blindness by demonstrating the presence of a normal optokinetic nystagmus.

Treatment Treatment is targeted at removing stressful events, reassuring the patient and providing a supportive role to help the patient gain conscious control over conflicts. Telling the patient that her symptoms are 'psychological' is not helpful.

KEY CONCEPTS

- *Conversion* is an unconscious process of transforming a psychic conflict into a somatic symptom.
- *Malingering* is a voluntary and conscious faking of symptoms.
- In *factitious disorders,* there is voluntary control over symptoms but the motive is subconscious.

10.6 Personality disorders

The set of characteristics that define the behaviour, emotions and thoughts of an individual are said to constitute that person's personality. These characteristics are also called traits. When personality traits are chronically inflexible and maladaptive, there may be associated impairment of social or occupational function and consequently subjective distress. The individual is then said to have a personality disorder.

Classification Personality disorders are among the commonest psychiatric disorders seen in clinical practice in the developed countries. They are grouped into three clusters due to the similarity of symptoms in the three categories. (Table 10.7). Cluster A disorders are characterised by eccentricity or oddity of behaviour. There is a tendency towards fantasy and psychotic thinking. Cluster B disorders are characterised by dramatic, erratic or emotional behaviour. Mood disorders are common in this category. Cluster C disorders are characterised by anxious and fearful behaviour patterns.

Clinical features The features of individual disorders are summarised in Table 10.6. Personality disorders tend to appear at adolescence and wane during middle age. They are self-limiting although the prognosis of individual disorders may be variable.

Treatment Personality disorders do not usually require drug treatment. Individual or group psychotherapy may be helpful.

Table 10.7 Characteristics of personality disorders

CLUSTER A

Schizoid	*Schizotypal*	*Paranoid*
Emotional coldness	Magical thinking	Hypervigilant–expects to be tricked
Loners, choose solitary activities	Social isolation	Social isolation
Dull and humourless	Peculiar speech–overelaborate without loosening of association	No sense of humour
Do not have eccentric thought, speech or behaviour	Eccentric behaviour	Exhibit pathologic jealousy
No interest in sex	Ideas of reference	Hostile, argumentative
	Paranoia or suspicion	Exaggerate problems

CLUSTER B

Histrionic	*Antisocial*	*Narcissistic*	*Borderline*
Dramatic, emotional erratic behaviour	Inability to accept guilt for destructive behaviour	Extremely sensitive to criticism	Impulsive unpredictable self damaging behaviour
Craving for attention	Truancy at school, work	Craving for attention	Mood instability
Excessively generalised and impressionistic speech	Lying, thieving	Exaggeration of achievements	Unstable interpersonal relations
Inability to put other's needs first	Fights and assaults people and animals	No capacity for empathy	Intolerance of being alone
Tantrums and angry outbursts	Chronic violation of rules	Arrogant behaviour	Inappropriate outbursts of anger
Overly concerned with appearance	Frequent change of jobs, marital partners	Excess sense of self importance and expects to be 'special' everywhere	Evaluating people as extremes—good and bad with no grey zones

CLUSTER C

Avoidant	*Dependent*	*Compulsive*	*Passive aggressive*
Low self esteem	Cannot initiate things	Perfectionist	Refuses to perform adequately at work
Social withdrawal	Seeks human contact	Inability to express affection	Intentional social inefficiency
Avoids new activities	Will agree to do unpleasant things to be liked	Insists on doing things his way	Makes mistakes on jobs he does not like to do
Has no close friends	Depends on others to decide for him	Indecision due to preoccupation with rules	Postpones things he does not like to do
Hurt by criticism	Hurt by criticism	Devotes time to work to the exclusion of social life	Stubborn, resents suggestions to improve

KEY CONCEPTS

- Personality disorder refers to relatively fixed, inflexible, maladaptive traits.
- Several types are described: *paranoid* (suspicious), *schizoid* (withdrawn), *schizotypal* (oddities of thinking), *histrionic* (attention-seeking), *narcissistic* (self-centered), *antisocial* (flouting norms), *avoidant* (low self esteem), *borderline* (unpredictable), *dependent* (seeking human contact), *compulsive* (perfectionist) and *passive aggressive* (procrastination).
- There is no definite treatment.

10.7 Drug abuse and alcoholism

Drug abuse refers to the intake of drugs at a dose and under circumstances that significantly enhance the potential for harm, whether or not such use is legal and whether it is intended to be therapeutic, pleasurable, consciousness-expanding or physician- prescribed. Several other terms need to be understood in this context. *Drug dependence* is a psychic state, and sometimes physical, resulting from intake of a drug; it is characterised by behavioural and other responses that always include a compulsion to take a drug on a continuous or periodic basis in order to experience its psychic effects and sometimes to avoid the discomfort of its absence. *Psychological dependence* is the development of a craving for a drug because its effects are perceived as pleasurable. *Physical dependence* is an altered physiological state induced by repeated drug intake and requires continued administration of the drug to prevent the emergence of a syndrome characteristic for each drug — a *withdrawal syndrome.* Two other terms used are habituation and addiction. *Habituation* is a state characterised by a desire to continue intake of the drug reflecting an underlying psychic dependence; there is no tendency to increase the dose and the habit is detrimental to the individual. *Addiction* is a state characterised by a compulsion to continue intake with a tendency to increase the dose reflecting psychic and physical dependence. This is detrimental not only to the individual but also to society at large.

Tolerance is used to describe the phenomenon where with repeated administration of the same dose of the drug there is a decreasing effect of the drug. This necessitates an increase in the dose on subsequent administrations in order to obtain the initial degree of effect. Table 10.8 provides a classification of psychoactive drugs.

Epidemiology and prevalence A large number of studies have been carried out in the northern states of Punjab, Uttar Pradesh and Rajasthan. Tobacco is the most widely abused drug overall (with a prevalence of 15–45 per cent) followed closely by alcohol (25–35 per cent). Next in frequency are the opioids and cannabinoids (4–15 per cent). Drug abuse has a male predominance. The majority of drug abusers belong to the student population with the prevalence in the various universities ranging from 20–35 per cent. The pattern of drug abuse is a little different in rural areas in that psychotropic drug abuse is infrequent. The use and abuse of drugs by medical students is higher than that among university students given the easy availability coupled with pharmacological knowledge about drugs.

Opioid Use

Opioids include morphine and other alkaloids of opium (such as codeine), semisynthetic opiate derivatives (such as diacetyl morphine or heroin) and synthetic morphine substitutes (such as pethidine or methadone). Opioid abuse is characterised by a strong psychic and physical

Table 10.8 Classification of psychoactive drugs

Class	Dependence		Tolerance	Duration (Hours)	Effects	Over-dose	Withdrawal
	Physical	Psychological					
A. *Narcotics*							
Opium	high	high	+	3–6	euphoria, drowsiness, respiratory depression, pinpoint pupils	slow shallow, breathing, convulsion, coma	watery eyes and nose, yawning tremors, cramps, sweating
Morphine	high	high	+	3–6			
Heroin	high	high	+	3–6			
Pethidine	high	high	+	3–6			
Methadone	high	high–low	+	12–24			
B. *Depressants*							
Barbiturates	high–moderate	high–moderate	+	1–16	slurred speech, drunken behaviour (without alcohol intake)	shallow breathing, dilated pupils, coma	tremors, insomia, delirium convulsion
Benzodiazepines	low	low	+	4–8			
Methaqualone	high	high	+	4–8			
Glutethimide	high	moderate	+	4–8			
C. *Stimulants*							
Cocaine	possible	high	+	1–2	euphoria, increased pulse rate and blood pressure, excitation	agitation, increased body temperature, hallucinations, convulsions	apathy, periods of sleep, depression
Amphetamines	possible	high	+	2–4			
Methylphenidate	possible	high	+	2–4			
D. *Hallucinogens*							
Lysergic Acid Diethylamide (LSD)	none	unknown	+	8–12 days	illusions and hallucinations, poor perception of time and distance	longer 'trips', psychosis	none reported
Phencyclidine	unknown	high	+				
E. *Cannabis*							
Marijuana	unknown	moderate	+	2–4	euphoria, relaxed inhibitions, increased appetite, disorientation	fatigue, paranoia	insomnia, hyperactivity, decreased appetite
Hashish	unknown	moderate	+	2–4			

dependence with development of marked tolerance and of cross-tolerance with related drugs.

Clinical features Morphine is the most commonly used opioid. It is used by sniffing or by injections (subcutaneous or intravenous). Administration by sniffing produces a sense of unusual well-being or euphoria. Intravenous use produces a 'kick' — warm flushing of skin and pleasurable sensations in the whole body.

The effects are, however, short-lived and the drug must be taken every few hours to avoid withdrawal symptoms. Heroin is 2–3 times more potent than morphine. Withdrawal symptoms are similar in both agents except for their temporal profile (Table 10.9). Drug abuse can be associated with other complications that may be due to non-sterile injection techniques (causing sepsis) or due to needle sharing (infections like hepatitis or AIDS) or due to allergic manifestations (ARDS). Some of these complications are enumerated in Table 10.10.

Treatment Treatment consists of drug withdrawal and methadone substitution when grade 2 signs (Table 10.8) appear. Methadone may be gradually tapered over the next ten days.

Cannabinoids

Cannabis is obtained from the hemp plant (Cannabis sativus). The highest cannabinoid concentrations are found in the flowering tops. The dried resinous exudates of tops is called 'charas' or 'hashish'. 'Bhang' is prepared from dried leaves and flowering shoots. 'Ganja' is the resinous mass from leaves and brackets of the inflorescence. The active principle is 9 tetrahydroannabinol (THC). 'Marijuana' is used to describe any plant part or extract.

The most common mode of cannabis intake is through self-administration by smoking. Bhang is consumed during festival occasions in India.

Clinical features Acute intoxication with cannabis induces a subjective perception of relaxation and mild euphoria. This is accompanied by a mild impairment of thinking, concentration, perceptual and psychomotor functions. There is mild bronchial irritation, tachycardia and conjunctival injection.

Chronic cannabinoid use results in the individual's loss of interest in common social goals with an increased devotion of time to drug acquisition and use. Cannabinoids do not cause a specific amotivational syndrome but long term use is associated with psychic and physical dependence. Withdrawal signs and symptoms in chronic users are typically mild and include tremors, sweating, nausea, vomiting, diarrhea, irritability and sleep disturbances. No treatment is usually required.

There is also a strong statistical association between the use of cannabis and other psychoactive drugs.

Cocaine Abuse

Cocaine is a central nervous system stimulant that is extracted from the leaves of the coca plant. It can be administrated by 'snorting' (inhalation) of the translucent powder, by intravenous injection, or by smoking of coca paste. Its use is uncommon in India.

Clinical features Cocaine use produces a brief dose-related stimulation. Chronic use can result in visual and auditory hallucinations and paranoid ideation. There is a psychological dependence and withdrawal can induce severe depression.

Amphetamine Abuse

Amphetamines are powerful CNS stimulants that also have respiratory stimulant, hypertensive and appetite-suppressant effects.

Clinical features The use of amphetamines leads to elevation of mood, reversal of fatigue and a postponement of sleep. High doses can result in psychotic behaviour with auditory and visual hallucinations and paranoid ideation. Long term use leads to tolerance as well as psychological dependence.

Lysergic Acid Diethylamide (LSD)

LSD produces CNS effects that start within two hours and last 8–14 hours.

Clinical features There is an increased perception of various stimuli with a distortion of

body image and loosening of ego boundaries. There may be 'flashbacks' with recall of various life events. If the subject is not prepared for such an experience, he may panic and fear that sanity is being lost. LSD causes psychic dependence and tolerance. Long term use is associated with somatic sympathomimetic effects.

Alcohol Use and Abuse

Alcoholism has been defined as both a chronic disease and a disorder of behaviour characterised by the drinking of alcohol to an extent that surpasses the social drinking customs of the community and that interferes with the drinker's health, interpersonal relations or means of earning livelihood. Dependence on alcohol is characterised by severe physical and psychic dependence.

Clinical features Alcohol intoxication consists of drunkenness, pathological intoxication, blackouts and coma. The correlation between blood levels and behavioural changes in casual drinkers is shown in Table 10.11.

Chronic alcohol intake is capable of affecting several systems of the body adversely. The liver

Table 10.9 Withdrawal syndromes associated with opioid dependence

Grade / symptoms and signs	*Onset (hours) after last dose*		
	Morphine	*Heroin*	*Methadone*
0. craving	6	4	12
1. yawning, perspiration, lacrimation, rhinorrhoea	14	8	34–48
2. mydriasis, pilo-erection, muscle twitches, muscle aches	16	12	48–72
3. insomnia, hypertension, fever, tachypnea, tachycardia, restlessness, nausea	24–36	18–24	–
4. vomiting, diarrhea	36–48	24–36	–

Table 10.10 Medical complications of opioid use

Category	*Complication*
1. Infections	septic injection sites abscesses, cellulitis, septic thrombophlebitis endocarditis, lung abscess, tetanus, AIDS, hepatitis B, D
2. Respiratory	pulmonary edema (ARDS)
3. Neurologic	overdosage coma, amblyopia, acute transverse myelitis, spinal epidural abscess, peripheral neuropathy, syndrome of inappropriate ADH secretion.

Table 10.11 Blood levels of alcohol and behavioural correlates

Blood levels (mg/100 ml)	*Behavioural changes*	*Blood levels (mg/100 ml)*	*Behavioural changes*
30	mild euphoria	50	mild intoxication
100	obvious ataxia	200	drowsiness
300	stupor	400	deep anesthesia
500	respiratory arrest and death.		

is the most commonly affected organ as oxidation of the alcohol is carried out by the alcohol dehydrogenase system and the microsomal ethanol oxidising system. Alcohol inhibits gluconeogenesis, damages cellular mitochondria and stimulates fatty acid synthesis and lactate production. Acute effects of excess alcohol consumption can culminate in alcoholic hepatitis. Chronic effects include cirrhosis with portal hypertension and its attendant complications. Other effects on the gastrointestinal tract include gastritis, peptic ulceration, pancreatitis and malabsorption of vitamins B_1, B_6, B_{12} and folate.

The chronic use of alcohol can result in cardiac toxicity manifesting either as an alcohol-induced cardiomyopathy or as arrhythmias, especially atrial arrhythmias (holiday heart syndrome). Alcohol use elevates blood pressure and alcohol modifies the lipid profile by elevating plasma levels of HDL cholesterol (a supposedly beneficial effect) and triglycerides (a deleterious effect). The skeletal muscle is not spared either, by alcohol consumption. An acute myopathy and myoglobinuria can result.

Alcohol is a bone marrow suppressant that suppresses erythropoiesis, granulopoiesis as well as thrombopoiesis. It impairs folate metabolism and facilitates the development of ringed sideroblasts in the bone marrow (known as sideroblastic anemia). Alcohol is toxic to the nervous system when it is abused chronically. A chronic distal sensorimotor peripheral neuropathy is the commonest feature. Other neurologic abnormalities include cerebrovascular accidents (hemorrhagic), a Wernicke-Korsakoff psychosis (due to concomitant thiamine deficiency), a pure cerebellar degeneration (especially of the vermis) and a syndrome characterised by myelin loss in the central pons (central pontine myelinolysis). It must be remembered while assessing an alcoholic subject with a neurologic deficit that alcoholics are prone to seizures as well as head injuries (with attendant complications like a subdural hematoma).

Alcohol withdrawal can result in a spectrum of symptoms; this is known as the *abstinence syndrome.* Coarse tremors and morning nausea-vomiting are the commonest features with a peak occurrence in the first 24 hours of withdrawal. Hallucinations may occur too: this is known as *alcoholic hallucinosis.* The hallmark of alcoholic hallucinosis is the clear sensorium despite the audiovisual hallucinations. Grand mal seizures, may occur in the first 48 hours — these are called *rum fits.* The most serious form of withdrawal is the syndrome of *delirium tremens* that manifests usually after 72–96 hours of abstinence. Delirium tremens is characterised by somatic, psychic and autonomic overactivity. The subject is agitated, sleepless, confused, overridden with delusions, hallucinations and tremors. There may be fever, tachycardia, diaphoresis, incontinence and dehydration.

Alcohol withdrawal syndrome is usually managed with supportive measures aimed at preventing or correcting dehydration and dyselectrolytemia. Thiamine is usually administered for control of seizures or for sedation. Though the syndrome is usually benign, delirium tremens can prove fatal in 5 per cent of patients.

Tobacco

Nicotine, one of the principal components of tobacco, is a highly addicting drug. Nicotine is associated with compulsive use (urge to smoke), psychoactive effects (smoking yields pleasure), drug-reinforcing behaviour (tobacco-seeking behaviour) and a withdrawal syndrome (cessation results in irritability, sleep problems, lethargy and headace).

Modes of use There are several forms of tobacco consumption. Although cigarette smoking is by far the most common form worldwide, other forms of tobacco consumption include smoking cigars, pipes, and bidis (tobacco wrapped in a temburni leaf), chewable products (tobacco, betel quid) and snorting (snuff).

Involuntary inhalation of cigarette smoke is referred to as *passive smoking*.

Epidemology The prevalence of smoking in India is about 50% in males and 3% in women. Beedi and hukka use are predominant in rural areas whereas cigarettes are the principal form of use in urban areas. There is a very strong dose-response relation between smoking and the health hazards associated with it. The risk of disease increases with an early age of initiation of the habit, the number of cigarettes smoked per day, the depth of inhalation and the duration of use.

Mechanism of harmful effects Tobacco smoke has over 4000 different compounds including nicotine, carbon monoxide, polynuclear hydrocarbons, and catechol. Some of these compounds are carcinogens or cocarcinogens. Cigarette smoking has been reported to be associated with mutations of the p53 gene (tumour suppressive gene), one of the most common mutations associated with various cancers. The p53 gene on chromosome 17 encodes a nuclear protein which binds and modulates genes involved in DNA repair, cell division and cell death. The p53 gene normally responds to unregulated cell growth by triggering cellular suicide (apoptosis).[1] Hence, smoking-induced mutations of the p53 gene can interfere with its normal regulatory function.

Health hazards Smoking is the most important preventable cause of morbidityand mortality in the developed world. It has been estimated that tobacco products account for about 3 million deaths per year at present. It has been further projected that this figure is likely to rise to 10 million by the year 2020, with 70 per cent of those deaths occurring in developing countries.

Smoking is associated with and causal for several health hazards. Smoking is associated with a two to three fold risk (compared to non-smokers) of fatal heart disease, stroke, peptic ulcer disease, fracturres (wrist, hip, vertebrae) and cataract. There is a ten fold greater risk of cancer of the lung, and a several fold greater risk of cancers of the oral cavity, esophagus, pancreas, kidney, urinary bladder, uterine cervix, and the head and neck region. Chronic obstructive airway disease is a major health problem faced by smokers. Although not causally related to hypertension, hypertensive smokers have a worse prognosis and an increased risk of accelerated hypertension. Smoking also is a causative factor for both atherosclerotic peripheral cascular disease and Buerger's disease (thromboangiitis obliterans). Women who smoke are at greater risk of giving birth to low weight infants. Smoking acts synergistically with oral contraceptives to significantly elevate the risk of stroke and subarachnoid hemorrhage in women who use hormonal contraceptive pills. About 20–30 per cent of heart attacks, strokes and cancers inn developed countries can be attributed to smoking as also about 80 per cent of lung cancer deaths and deaths due to chronic obstructive airway disease.

Passive smoking is also a serious health hazard. It is associated with increased risk of coronary disease and lung disease. Children whose parents smoke are more likely to smoke themselves and are at increased risk of chronic middle ear infections, and respiratory tract infections.

Smoking Cessation Cessation of smoking is associated with major health benefits even in long-standing smokers. The increased risk of heart attacks falls rapidly within the first two years and normalises over the first five years, with a small residual risk persisting in longstanding smokers. The elevated risk of lung cancer takes longer to fall after cessation of smoking; it decreases over 10–15 years, with a residual risk persisting in longstanding smokers.

1 Apoptosis is also called programmed cell death. In this process the nucleus and cytoplasm of the cell condense and the cell fragments are engulfed by surrounding macrophages.

Important steps in initiating smoking cessation include motivating the patient to quit, actually setting a date, evaluating and treating any withdrawal symptoms, and maintaining follow-up to reinforce the message. Withdrawal symptoms may be treated with nicotine gum or transdermal patches, though these agents are not easily available in India. Clonidine and buspirone may be used to as adjuncts to treat some of the withdrawal symptoms.

Community measures Important steps for tobacco control include targeting current smokers, reducing passive smoking (avoidance of smoking at public places, places of work, transportation), educating children and adolescents (the peak age of initiation of the habit), eliminating tobacco advertisements, displaying prominent health warnings on all tobacco products and exploring viable economic alternatives to tobacco production and trade.

KEY CONCEPTS

Drug dependence

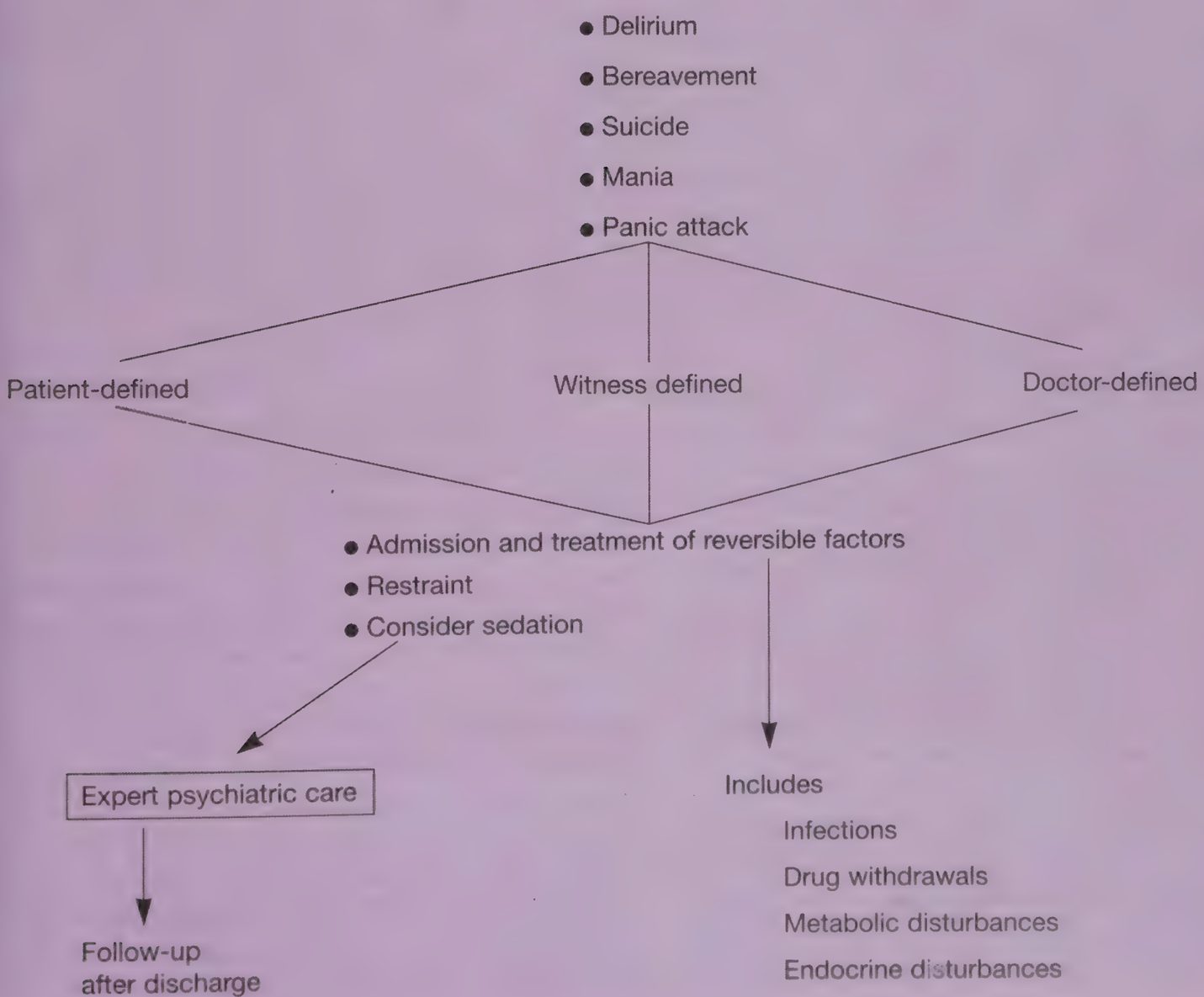
- Drug dependence is of two types: *psychologic* (desire to repeat to obtain pleasure) and *physical* (when abstinence produces a *withdrawal syndrome*).
- Cocaine, marijuana, amphetamines, and LSD produce chiefly psychic dependence. Opiates, alcohol and barbiturates produce both psychic and physical dependence.

Alcohol

- This is a drug associated with clinical toxicity along with the hazard of physical dependence and a dangerous abstinence syndrome.
- *Clinical toxicity* affects various systems such as *hepatic*: fatty liver, hepatitis, cirrhosis, *CVS*: hypertension, cardiomyopathy, atrial tachyarrhythmias; *GI*: esophagitis, gastritis, pancreatitis (acute and chronic); *CNS*: intoxication, Wernicke-Korsakoff syndrome (amnesia and confabulation), peripheral neuropathy; and *endocrine*: gynecomastia, amenorrhea.
- The clinical picture may be dominated by work-related and social problems. LFT may be deranged with AST/ALT>2:1. Macrocytic anemia may be evident on peripheral smear examination.
- *Treatment* includes counselling and support to help maintain abstinence. Withdrawal syndromes must be treated promptly; parenteral thiamine is advised for Wernicke-Korsakoff psychosis.

10.8 Psychiatric emergencies

Management of psychiatric emergencies



11

Disorders of the Respiratory System

11.1 Anatomical and physiological considerations

The Upper Airway

The inspired air traverses the nose, the pharynx, the larynx and the tracheobronchial tree successively before it reaches the alveoli. After passing through a coarse filter of vibrissae just within the nares, the inhaled airstream enters the nasal cavity. The nasal cavity is narrowed by the protruding *turbinates* and this accounts for roughly half of the normal inspiratory resistance. The inspiratory stream then abruptly changes direction by 90 degrees into the nasopharynx, resulting in turbulent airflow. This results in the removal of particles larger than 10 μm by a process called *inertial impaction.* Large collections of lymphoid tissue, including the tonsils and the adenoids, are placed strategically around the site of particle impaction in the nasopharynx and constitute the *Waldeyer's ring.* The highly vascular nasal mucosa also serves to warm and humidify the inhaled air. It also produces a steady flow of mucoid secretions, supplemented by the paranasal sinuses. The direction of mucociliary flow is mostly posterior, so that the mucous with the impacted particles is normally swallowed. Nerve receptors in the nasal mucosa provide yet another mechanism to expel obnoxious stimulants — the *sneeze reflex.*

From the nasopharynx the inspired air passes through the larynx. The larynx is narrowest at the plane of the true vocal cords and contributes significantly to ventilatory resistance. Apart from its vital role in phonation, the larynx protects the airway from aspiration during swallowing and is vital for the cough reflex. The intrinsic laryngeal muscles are innervated by the recurrent laryngeal branch of the vagus nerve. Neuromuscular dysfunction of the larynx predisposes to aspiration-related problems such as aspiration pneumonitis. Conversely, since the intrathoracic part of the recurrent laryngeal nerve passes under the aortic arch on the left side and in relation to the subclavian artery on the right, intrathoracic pathology can lead to laryngeal dysfunction.

The Lungs and Central Airways

The lungs are paired structures, each weighing about 400 grams, which lie in the pleural cavities and are invested with a translucent layer, the visceral pleura. The right lung is slightly larger than the left and is divided by oblique and horizontal fissures into three lobes; the left lung has only two lobes. In about one per cent of the population, a part of the right upper lobe is separated from the rest by a fissure containing the azygos vein and it is then known as the *azygos lobe.* At the hilum of each lung, the bronchi, blood vessels, nerves and lymphatics enter or leave the lung.

The trachea, a fibrocartilaginous tube about 12 cm long, divides at the *carina* into a wide, short, vertical right bronchus and a longer, more

oblique left bronchus. The right bronchus is also surrounded by a cuff of lymphoid tissue which drains the entire right lung and the inferior part of the left lung. This anatomical arrangement explains why foreign bodies are more likely to lodge in the right lung and why the right middle lobe is prone to a repeated 'infection-obstruction-collapse' cycle known as the *right middle lobe syndrome.* The right bronchus has three lobar branches, the left has only two. *Lobar bronchi* divide into *segmental bronchi,* each of which defines a *bronchopulmonary segment.* There are ten bronchopulmonary segments in each lung. The segmental bronchi undergo further dichotomous branching. There are about 25 divisions between the trachea and the terminal respiratory bronchiole. The initial seven divisions have a pseudostratified columnar epithelial lining with goblet cells, submucosal mucous-secreting glands, cartilage and a smooth muscle layer. They also contain specialised neurosecretory cells, the *K cells or Kulchitsky cells,* that secrete 5-hydroxytryptamine and other mediators such as bombesin. Over the next 16–18 divisions, the cartilage and goblets cells disappear; the smooth muscle layer thins out and granulated *Clara cells* (that probably secrete surfactant) become abundant. The terminal bronchioles end in *respiratory bronchioles.*

The tracheobronchial tree produces respiratory mucous, a 5 μm sheet across the entire respiratory epithelium. This mucous blanket is the *gel phase* and is kept elastic by the movement of cilia which move the blanket, along with the particles trapped in it, up towards the larynx (*mucociliary escalator*). Most of the mucous is produced by the submucosal glands, although the goblet cells also contribute. In conditions like chronic bronchitis, a marked hypertrophy of submucosal glands underlies the constant expectoration of sputum. The normal pH of this mucous is 7.4; a lower pH (as seen in asthmatics) leads to a loss of buffering capacity and an increased susceptibility to damage by environmental acid exposure. The cilia have a beat frequency of 20 per second, retracting into a periciliary fluid (the *sol phase*) that differs from mucous. The periciliary fluid contains serum compounds (Ig), salts, inflammatory mediators and mast cells. Each cilium consists of two paired central tubules joined by spokes, to nine peripheral tubules (doublets) which in turn are linked together by 'nexin' links (Fig 11.1). Each doublet has a peripheral 'dynein' arm that contains ATPase. The doublet filaments slide over one another and bend to produce ciliary motion, the central tubules having a co-ordinating function. In the dyskinetic cilia syndromes, the cilia do not move properly (or sometimes, do not move at all) due to absent dynein arms. The result is diminished muco-ciliary transport and an increased incidence of infections leading to bronchiectasis, as in the *Kartagener syndrome* (see chapter 11.6).

The airways and alveolar tissue distal to the terminal (or last) non-respiratory bronchiole, is the *acinus.* The respiratory bronchioles divide three or four times and then give rise to *alveolar ducts*. Alveolar ducts terminate in *alveolar sacs*. Each respiratory bronchiole leads to 200 alveoli.

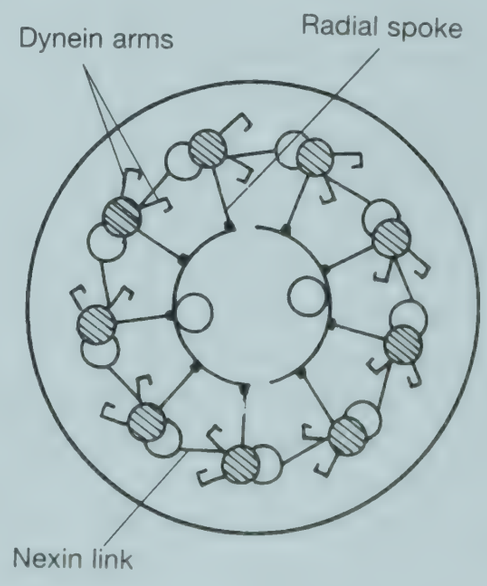


Fig 11.1 The structure of the cilium consists of two central microtubules surrounded by a ring of nine double microtubules. The central microtubules are linked to the peripheral ones by radial spokes and each peripheral pair of microtubules is attached to its neighbour on either side by the nexin links. There are also projections from the peripheral microtubules called dynein arms.

There are over 300 million alveoli in the lungs, having a total surface area of 40–80 m^2. The alveoli are polyhedral structures lined mostly by simple squamous epithelium or the *Type I pneumonocytes.* About 1–10 per cent of the alveolar surface is covered by larger cuboidal cells, with osmiophilic inclusions — the *Type II* or *granular pneumonocytes.* They secrete the surface-active phospholipid complex called *surfactant,* the major component of which is *dipalmitoyl phosphatidyl choline.* They also proliferate in response to injury to the alveoli. Capillaries are the other major component of the alveoli. They are lined by endothelial cells resting on a basement membrane which is structurally distinct from, but frequently in close contact with, the basement membrane of the alveolar epithelial cells. The interstitium of the alveolar septum is the part between the two basement membranes. It contains collagen, fibroblasts, alveolar macrophages, contractile fibroblasts (myofibroblasts), lymphocytes and plasma cells. The alveolocapillary barrier thus comprises the alveolar epithelium, the capillary endothelium and the interstitial space in between them. It is about 0.50 μ thick. Adjacent alveolar spaces are connected through openings in the alveolar wall known as the *pores of Kohn.* These pores ensure 'collateral' ventilation. Similar collateral channels exist between the terminal bronchioles and alveolar lung tissue and are known as the *canals of Lambert;* these are especially prominent in pulmonary fibrosis. The alveolar macrophages are derived from bone marrow precursors and migrate out of the bloodstream. They have receptors for IgG and C3, can synthesise complement, α_2-macroglobulin and interferon, and can both promote and inhibit immune reactions. *α_1-antitrypsin* is a protease inhibitor which inhibits the elastolytic activity of neutrophils; it is also present in the lung.

The lung receives its blood supply from two sources: the bronchial circulation and the pulmonary circulation. The bronchial arteries, usually one on the right and two on the left, are branches of the thoracic aorta. The bronchial veins drain about a third of the bronchial circulation. They open into the azygos venous system. The remaining two-thirds of the bronchial circulation drain into the pulmonary veins and constitute a physiological right-to-left shunt. The pulmonary circulation is unique in more than one way. It is a low pressure circuit with a mean pulmonary artery pressure < 20 mmHg. This is a consequence of the low resistance of the pulmonary vascular bed. The resistance of a vascular bed is a function of the cross-sectional area of the perfused bed. The large cross-sectional area of the pulmonary capillaries and the ability of the vascular bed to expand by recruiting 'non-perfused' vessels, thus accommodating any increase in flow, account for the low pulmonary vascular resistance. Another peculiarity of the circuit is the gravity-dependent perfusion (Fig 11.2), by which lung bases receive more flow compared to the apices. At the apex, the pulmonary capillary pressure is just about equal to the alveolar pressure so that the flow is barely maintained. As the pulmonary artery pressure increases from the apex to the base, the driving force becomes the difference between the pulmonary arterial and venous pressures as soon as the latter exceeds alveolar pressure. Blood flow at the base is increased due to a lower vascular resistance there (due to dilatation of vessels consequent to an increased *transmural pressure,* alveolar pressure being gravity-independent and therefore constant); this increase is not due to a change in driving forces since gravity causes an equivalent increase in both arterial and venous pressures. The mean pulmonary capillary hydrostatic pressure is 6–9 mmHg and the colloid oncotic pressure is 25 mmHg, which serves to keep the alveoli dry. The volume of blood in the pulmonary vessels at any time is about 1 litre, of which 100 ml is in the capillaries: this is the *pulmonary capillary blood volume.* The pulmonary veins are important distensible reservoirs. In the supine position,

pulmonary blood volume may increase by upto 400 ml, thereby causing a decrease in vital capacity. This explains the orthopnea of congestive heart failure. Unlike the systemic circulation where hypoxia causes vasodilation, the response to alveolar hypoxia is pulmonary vasoconstriction, a mechanism meant to restrict 'wasteful' perfusion of poorly ventilated alveoli. The vasoconstrictor response also raises pulmonary vascular resistance. The presence of

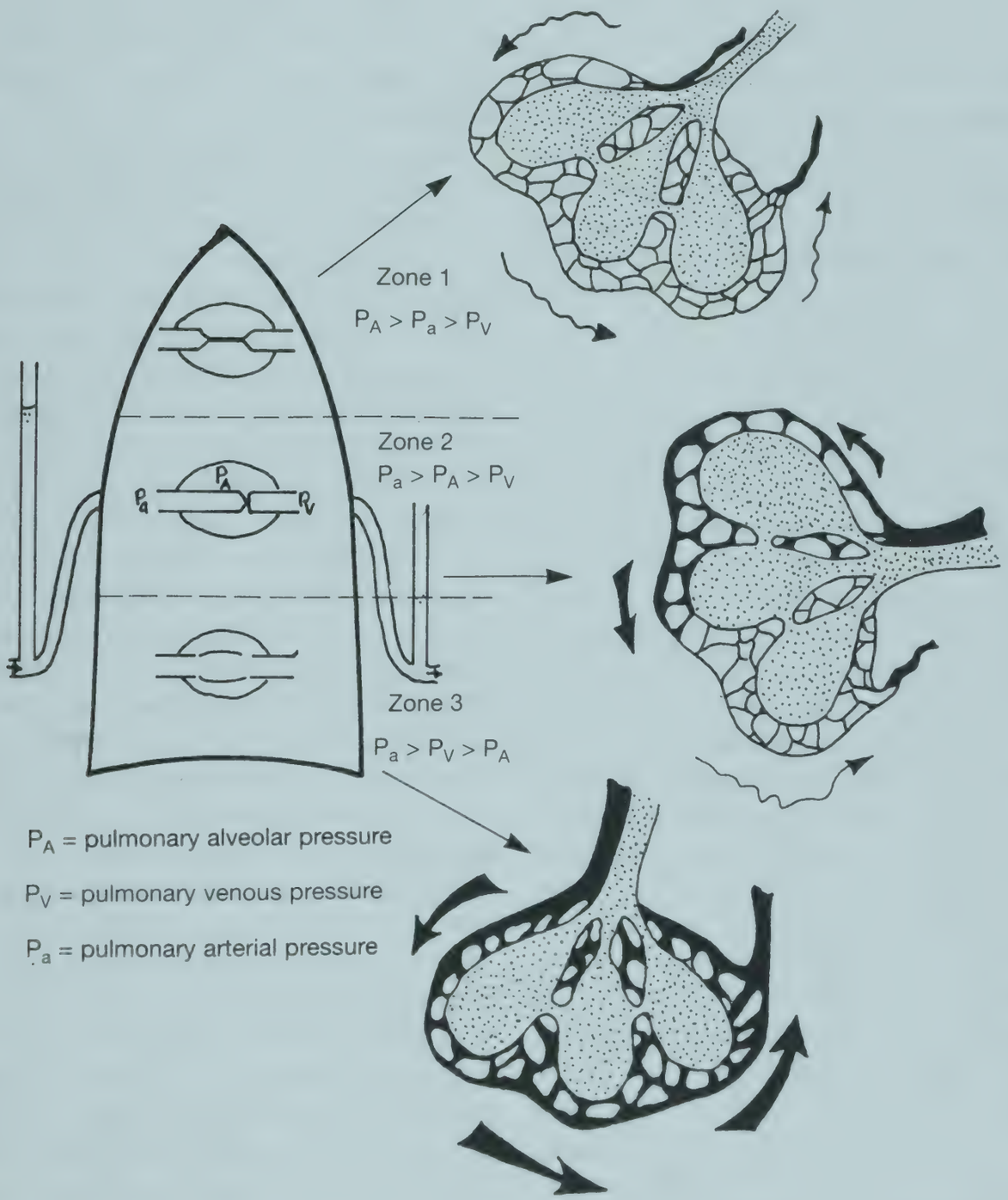


Fig 11.2 Gravity-dependent perfusion of acinar units. In the upper zone, alveolar pressure (P_A) is higher than pulmonary artery pressure (P_a) so that the capillaries are virtually empty. In the midlung, alveolar pressure (P_A) is lower than arterial pressure (P_a) but higher than venous pressure (P_V), so that blood flow occurs through the arterial end of the capillaries but is impeded on the venous end. The unit at the base of the lung shows dilated capillaries throughout since both arterial (P_a) and venous (P_V) pressures are greater than alveolar pressure (P_A).

anastomoses between the bronchial and pulmonary circulations at the arterial, capillary and venous levels is another peculiarity of the pulmonary circuit.

Although insignificant in the healthy state, bronchial-pulmonary artery anastomoses develop in disease states (like fibrosis, bronchiectasis), with the flow from bronchial to pulmonary vessels increasing vascular resistance in the damaged underventilated areas. The bronchial-pulmonary venous anastomoses become engorged in mitral stenosis; rupture of these anastomoses is one of the causes of hemoptysis in this condition.

Ventilation

The diaphragm is the major muscle of inspiration. Its contraction increases the anteroposterior, vertical and transverse diameter of the thorax. Its central *crural* portion is innvervated by the phrenic nerve (C3,4,5) and its lateral *costal* portion by the intercostal nerves (T6–T12). Paralysis of both leaves of the diaphragm may not cause significant disability in subjects with non-diseased lungs as the external intercostal muscles, scalene muscles and sternomastoids take over the inspiratory function. The sternomastoids assist by elevating the thoracic cage. With inspiration, the intra-thoracic volume increases, pleural pressure falls and intraalveolar pressure becomes subatmospheric (1–3 mmHg). This causes the air to enter the lungs. Expiration is primarily a passive process, due to the intrinsic elastic recoil of the lungs and the chest walls. The internal intercostal muscles also play a minor contributory role. The lungs and the chest wall both have significant elastic recoil. The elasticity of the lungs is partly related to the surface active tension in the alveoli (2/3) and partly to the elastic fibres of the lung parenchyma (1/3). The relationship of the change in volume to the change in pressure (DV/DP) is *compliance*. Compliance varies inversely with the *elastance*, being roughly 200 ml/cmH_2O, for the lungs. Compliance of the chest wall is also about 200 ml/cmH_2O. The lungs and the chest wall recoil in opposite directions, the respective forces equalising at the *functional residual capacity* (FRC) of the lung (which is a little less than 50 per cent of the total lung capacity). Lung compliance is decreased when the lung is stiffer (due to fibrosis or infiltration) and is increased when the elastic recoil is reduced (as in emphysema).

During quiet breathing, most of the work of the respiratory muscles is to overcome the elastic resistive forces. At higher breathing rates, airway resistance too has to be overcome. Roughly 40 per cent of this airway resistance is present at the larynx, 45 per cent at the large airways and 15 per cent at the peripheral small airways (which are 2 mm in diameter). The work of breathing can, therefore, be increased by significant increases in elastic or airway resistance. When elastic resistance is increased (as in fibrosis, or chest wall deformity), respiration tends to become rapid and shallow. This is because even small increases in tidal volume increase the amount of work required to overcome elastic resistance, whereas a higher respiratory rate reduces it. When airflow resistance is increased, respiration tends to be slower and deeper. This is because a higher respiratory rate increases the work done to overcome airway resistance whereas an increased tidal volume reduces it. The normal work of breathing accounts for only 4–5 per cent of total energy consumption of the body.

Alveolar ventilation is also gravity-dependent. Since there exists a gradient for pleural pressure (which is most negative at the apex, and less negative at the bases of the lungs), alveoli at the apex are more inflated than those at the base at the start of inspiration; lung bases are more ventilated: since alveoli are smaller, they are more distensible, that is, they fall on the steep portion of the compliance curve. The effects of gravity on perfusion, however, outweigh those on ventilation, so that the apices

are overventilated and the bases underventilated, relative to the circulation. Ventilation involves the integrative function of the *brainstem control centres* with the respiratory *sensors* and *effectors*. The ventral medullary reticular formation has a group of ill-defined neurons which generate the rhythmicity of respiration. The pons contains an *apneustic centre* which adjusts the ratio of inspiratory time to expiration time; uninhibited activity leads to sustained inspiratory spasm or apneusis. A *pneumotaxic centre* regulates the rate of inspiration. The cerebral cortex exerts voluntary influences that can modulate the activity of all these centres. The importance of these centres is revealed by the hypoventilation which accompanies medullary compression and the hyperventilation which is associated with pontine and midbrain lesions (also known as the central neurogenic hyperventilation response). The respiratory sensors include the *central chemoreceptors* in the ventral medulla which are sensitive to hypercarbia and acidosis and to a lesser extent to hypoxemia, and the *peripheral chemoreceptors* (aortic and carotid bodies) which are most sensitive to hypoxemia and less sensitive to hypercarbia. The respiratory sensors also include the chest wall mechanoreceptors, airway irritant receptors, pulmonary stretch receptors which mediate the inhibito-inspiratory *Hering-Breuer reflex,* and the *juxtacapillary 'J' receptors* which respond to vascular congestion.

Gas Transport and Transfers

In the blood, 98 per cent of the oxygen is transported in combination with hemoglobin (1.34 ml O_2/gm Hb); a small amount is dissolved in plasma (0.003 ml O_2/100 ml blood/ mmHg PO_2). Ninety per cent of carbon dioxide is transported as bicarbonate, the rest being combined with hemoglobin as a *carbamino* compound. The relation between PO_2 and O_2 content is the sigmoid-shaped oxyhemoglobin dissociation curve; the curve shifts to the right with increases of PCO_2 (*Bohr effect*)[1], temperature, 2,3-DPG levels and H+ ion concentrations, thus expediting oxygen release. The relationship of PCO_2 and CO_2 content is the steep and linear carbon dioxide dissociation curve; the curve shifts to the right with increased PO_2 (*Haldane effect*)[1] that helps unload CO_2.

Alveolar gas pressure reflects the sum of the partial pressure of oxygen, carbon dioxide, nitrogen and water vapour. Since the partial pressure of water vapour and total alveolar gas pressure are relatively fixed, the PO_2 and PCO_2 vary inversely according to the *alveolar gas equation.*

$$P_AO_2 = \text{Inspired } PO_2 - \frac{P_A\,CO_2}{(RQ)}$$

$$= P_iO_2 - 1.25PCO_2$$

(assuming an RQ of 0.8)

where RQ = respiration quotient and where P_A = alveolar partial pressure of oxygen/ carbon dioxide

Thus an increase in P_ACO_2 results in a decrease in P_AO_2. Since CO_2 is highly soluble, $P_aCO_2 = P_ACO_2$.[2] Oxygen being less soluble and less diffusible, P_aO_2 is usually 5–10 mm less than P_AO_2 even normally. An increase in $P_AO_2 - P_aO_2$ (*alveolar arterial difference*) results in hypoxemia. Hypoxemia can also occur with hypoventilation, leading to increased P_ACO_2 and a reciprocal fall in P_AO_2 and thus, of P_aO_2. In this case, however, the alveolar arterial PO_2 difference is not increased. An increased $P_AO_2 - P_aO_2$ difference can occur due to abnormalities of diffusion, an abnormal ventilation-perfusion ratio or due to intrapulmonary or intracardiac shunts. *Diffusion* across the

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[1] The Haldane effect contributes to 46 per cent of basal CO_2 exchange whereas the Bohr effect contributes to only 2 per cent of O_2 release.

[2] P_AO_2 = alveolar partial pressure of oxygen
P_ACO_2 = alveolar partial pressure of carbon dioxide
P_aO_2 = pulmonary arterial partial pressure of oxygen
P_aCO_2 = pulmonary arterial partial pressure of carbon dioxide

alveolocapillary membrane is influenced by differences in partial pressures of the gas in the alveoli and pulmonary veins, the total area and the thickness of the membrane, the number of red blood cells and their transit time in the pulmonary capillaries. Diffusion defects can be caused by obstruction to airway entry, dilatation and confluence of respiratory bronchioles resulting in an increased pathway for diffusion (as in centrilobular emphysema), the loss of capillaries, thickened alveolocapillary membrane (known as pulmonary fibrosis), replacement of air space by edema or exudate (known as pulmonary edema, consolidation) and anemia.

Respiratory Sounds

The normal breath sounds auscultated with a stethoscope are termed *vesicular* breath sounds. Vesicular breath sounds are due to turbulent flow in large airways filtered through the alveoli. The inspiratory component is longer than the expiratory component and there is no gap between the two components. *Bronchial* breath sounds occur due to turbulent flow in large airways which is not filtered through the alveoli. These sounds have a hollow, blowing character. The inspiratory and expiratory components of bronchial breath sounds are equal in duration and they are separated by a gap. Bronchial breath sounds are heard over an area of consolidation, pulmonary fibrosis, or lung collapse and above a pleural effusion.

Adventitious sounds are additional breath sounds that occur in disease states. They may be continuous or intermittent (within a phase of respiration). Examples of such continuous adventitious breath sounds are *wheezes.* Wheezes have a musical quality and may be expiratory or inspiratory, or both, and usually indicate airway obstruction. Expiratory wheezes are usually louder. Inspiratory wheezes indicate a severe degree of airway obstruction. A localised wheeze with a fixed musical note (monophonic) suggests a fixed underlying airway obstruction (such as due to an obstructing neoplasm). Intermittent sounds are also described as *crackles.* Crackles are non-musical in quality. Early inspiratory crackles suggest small airway disease as in chronic obstructive airway disease. Late or paninspiratory crackles arise in the alveoli. They may be fine (as in pulmonary fibrosis), medium (as in left ventricular failure) or coarse (as in bronchiectasis).

11.2 Approach to a patient with respiratory disease

Approach to a Patient with Cough

Physiology Cough is a reflex response of the airways. The afferent arm of the reflex originates from epithelial receptors in the airways. The afferent impulses travel through the vagus nerve to medullopontine integrative centres. The efferent pathway involves cholinergic nerves to the diaphragm, the intercostal and abdominal muscles. There are three phases in the response: an initial phase, wherein the glottis is open, is followed by a compressive phase which is initiated by closure of the glottis. The third phase begins with sudden opening of the glottis with an explosive expiratory flow. The three phases produce high flows and a decreased cross-sectional area — the resultant high linear velocity is effective in clearing irritant particles.

Table 11.1 Causes of chronic cough

A. **Upper airway origin**
Sinusitis
Post nasal drip
Nasal polyps
Chronic pharyngitis
Chronic rhinitis
B. **Lower respiratory origin**
Asthma
Chronic obstrutive airway disease
Bronchiectasis
Tumour
Foreign body
Chronic infection, e.g. tuberculosis
C. **Cardiac origin (often nocturnal)**
Left heart failure (of whatever cause)
Aortic aneurysm
Pulmonary embolism
D. **Mediastinal origin**
Lymphadenopathy with extrinsic tracheal compression
E. **Gastrointestinal origin** (cough with swallowing)
Aspiration
F. **Psychogenic**

Etiology The various causes of chronic cough are listed in Table 11.1. Chronic bronchitis, pulmonary tuberculosis and bronchiectasis are among the three commonest causes of a chronic cough in our country. Smoking, especially cigarette or bidi smoking, is one of the commonest contributory factors in the pathogenesis of chronic cough.

Diagnostic evaluation

A thorough clinical history, with emphasis on smoking habits, occupational or environmental exposure or an allergic predisposition, yields useful clues to the etiology of a chronic cough.[1] The presence or absence of fever, the nature and amount of the expectorated sputum may aid the diagnosis of pulmonary tuberculosis and bronchiectasis respectively.

Nocturnal cough suggests a possible cardiac cause while an association with swallowing suggests recurrent aspiration. A non-productive

[1] The character of the cough may help suggest etiology such as, a 'brassy' cough in tracheal disorders or a 'bovine' cough in laryngeal disease.

cough suggests extrinsic compression of the tracheobronchial tree, pulmonary infiltration/fibrosis, or a pharyngeal origin of the cough (smoker's cough).

Physical examination must include a meticulous assessment of the nose, mouth, ears, throat, sinuses, lungs and the cardiovascular system. Based on the clinical findings and history, a chest radiograph, X-ray of paranasal sinuses and sputum examination (for acid-fast bacilli) may be contemplated. Endobronchial disease, however, can exist despite a normal roentgenogram.

Complications Paroxysms of cough may lead to rib fractures, pneumothorax, subconjunctival hemorrhage or syncope. Cough syncope is a brief loss of consciousness after a bout of cough. It is seen in obese male smokers, and the pathogenetic mechanisms include cerebral hypoperfusion, inhibition of midbrain reticular areas and a 'concussion-like' effect of rapid rises in cerebrospinal fluid pressure during the cough bouts.

Treatment The specific treatment is directed at the underlying cause itself. The symptomatic treatment includes use of antitussive agents for suppression of a troublesome, non-productive cough. Some antitussive agents may act peripherally (such as a local anesthetic applied on mucous membranes) while others like codeine, act on the central medullary integrative centres. Productive coughs are treated with physiotherapy and proper hydration. Expectorants and mucolytic agents are of doubtful efficacy (Table 11.2).

Table 11.2 Treatment of cough

Category	*Mechanism of action*	*Agent*	*Dose/Comments*
I **Antitussives**	suppress cough		
A. centrally acting	suppress cough reflex by depressing medullary cough centre	a) Codeine	10–20 mg q 4–6 hours
		b) Dextromethorphan	15–30 mg q 6hours
B. peripherally acting	act on afferent or efferent side of cough reflex	a) demulcents licorice, glycerine	given as syrup or lozenges
		b) local anesthetics benzocaine	as lozenges or as sprays before procedures
		c) humidifying aerosols	
II **Expectorants**	help expel bronchial secretions		
A. mucolytics	have free sulphydryl groups that open mucoprotein disulphide bonds, reducing sputum tenacity	a) acetylcysteine	10–20% solution, nebulised; restricted use to chronic bronchitis, cystic fibrosis
B. proteolytic enzymes	liquefy sputum	a) pancreatic dornase	grossly purulent sputum
C. iodides	liquefy sputum	a) potassium iodide	0.5–4 ml q 6 hours
		b) iodinated glycerol	60 mg q 6 hours
D. syrup of ipecac			0.5 ml qs.
E. guaifensin	no clear cut evidence of efficacy		100–200 mg q 4 hours

* The use of most expectorants is controversial with scanty objective evidence of decrease in the amount, viscosity or ease of expectoration. Traditional expectorants not included in the table are ammonium chloride, terpin and creosote. Their efficacy is doubtful at the doses found in most cough remedies.

Approach to a Patient with Dyspnea

Dyspnea refers to a 'subjective' awareness of breathing. It is not like tachypnea (rapid breathing) which can be assessed objectively. The extent of 'awareness' may vary from person to person depending on his/her genetic content, life experiences, emotional needs despite an identical form of stress.

Pathophysiology The various causes of dyspnea are depicted in Table 11.3. The neural pathways by which dyspnea is sensed involves receptors in the respiratory muscles as well as in the lung parenchyma. It has been suggested that whenever the length-tension relations in the respiratory muscle spindles are inappropriate, neural traffic to the central nervous system from these receptors results in the perception of dyspnea. Dyspnea is also sensed due to stimulation of a number of interstitial non-myelinated vagal type C fibres (including the J receptors).

In patients with pulmonary disease, dyspnea is often related to an increased work load during breathing. Whenever the lungs or chest wall are stiffer than normal (as in pulmonary fibrosis), or when the resistance to airflow is increased (as in obstructive airway disease), a greater inspiratory muscle tension is required to produce a tidal breath. This is perceived as dyspnea. Patients with cardiac dyspnea often have nocturnal dyspnea. This may be related to nocturnal redistribution of blood from the peripheral vascular compartments, a reduction in the vital capacity due to a raised diaphragm and a decrease in bronchodilator tone during the REM phase of sleep.

Evaluation A careful history and clinical examination usually provides clues to the etiology of dyspnea. Thus, a diagnosis of anemia, extreme obesity, chronic obstructive airway disease or a cardiac etiology can be recognised easily. It may be difficult to make the distinction between a cardiac cause and a pulmonary cause on occasion; wheezing may be found in cardiac dyspnea and cardiac dyspnea may mimic a restrictive lung disease. Associated findings of a raised jugular venous pressure, cardiomegaly, an audible S_3 or murmur and electrocardiographic evidence of infarction, ischemia (old or fresh) or left ventricular hypertrophy would favour a diagnosis of *cardiac asthma.*

A history of fever, purulent sputum, pleuritic chest pain and signs of consolidation (bronchial breath sounds, increased tactile and vocal

Table 11.3 Differential diagnosis of dyspnea

Acute dyspnea	*Chronic dyspnea*
Pulmonary causes	**Pulmonary causes**
pneumonia	chronic obstructive airway disease
pulmonary thromboembolism	restrictive lung disease (see Chapter 11.5)
pneumothorax	primary pulmonary hypertension
obstructive airway disease	
foreign body aspiration	
Non-cardiogenic pulmonary edema	**Non-pulmonary causes**
high altitude pulmonary edema	congestive cardiac failure
noxious gas inhalation	anemia
neurogenic	hyperthyroidism
sepsis	upper airway disease
fat embolism	extreme obesity
other causes of ARDS (see Chapter 11.4)	psychogenic
	cardiogenic pulmonary edema (see **Cardiology** section)

fremitus, egophony along with crepitations) suggest pneumonia. A history of prolonged immobilisation, recent surgery, past or present venous thromboses or intake of oral contraceptives may suggest a diagnosis of pulmonary embolism if other clinical findings such as hemoptysis, a pleural friction rub, a right-sided third heart sound, mild fever, tachycardia, tachypnea and electrocardiographic evidence of right ventricular strain are corroborative. A sudden onset of chest pain or dyspnea precipitated by strenuous exertion, coughing or air travel alongwith physical findings of hyperresonance, decreased breath sounds and contralateral tracheal shift would suggest a diagnosis of pneumothorax. A history of foreign body aspiration is usually available in a conscious adult with such a preceding event; this should always be considered as a diagnostic possibility in a child with localised wheezing. In an unconscious patient with a sudden onset of dyspnea, a possibility of vomiting with aspiration must be considered. A history of accidental exposure to a noxious gas such as, chlorine, phosgene, or smoke can cause acute dyspnea and is often accompanied by conjunctivitis, pharyngitis, bronchitis and wheezing. A sudden ascent to a high altitude without prior acclimatisation can result in acute dyspnea with clinical evidence of bibasilar rales; this is known as high altitude pulmonary edema. Neurogenic pulmonary edema is seen in epileptic patients after a seizure and in patients with increased intracranial pressure.

Investigations A chest roentgenogram and electrocardiogram can be obtained to provide additional diagnostic clues to the etiology of dyspnea. Blood counts are crucial if pneumonitis is a strong possibility and a ventilation perfusion scan can be sought if a diagnosis of acute pulmonary embolism is likely. The chest X-ray can differentiate a lobar pneumonia from a pneumothorax and pulmonary edema (bihilar haze: butterfly pattern). The electrocardiogram may be diagnostic if it demonstrates myocardial infarction. Although findings of right axis deviation, an *$S_1Q_3T_3$ pattern* (see cardiology section) or right ventricular strain provide supportive evidence of a diagnosis of pulmonary embolism, they may be seen on occasion in any case of acute dyspnea. Arterial blood gases are helpful in management decisions in the acutely breathless patient but are of limited use in differentiating the various diagnostic possibilities under consideration.

Treatment Treatment depends on the identified etiology of dyspnea. Thus, antibiotics may be administered for bacterial pneumonia, diuretics and morphine for cardiogenic pulmonary edema, bronchodilators for obstructive airway disease, fibrinolytic therapy or anticoagulants for thromboembolism, intercostal drainage may be required for a pneumothorax, and bronchoscopy for the retrieval of a foreign body. Supplemental oxygen will be of help in all patients with clinical or laboratory evidence of hypoxemia.

Clubbing

Clubbing is a deformity of fingers and toes in which the distal phalanx progressively assumes a bulbous or 'clubbed' appearance. The various causes of clubbing are shown below.

Table 11.4 Causes of clubbing

Respiratory
bronchiectasis
interstitial lung disease
bronchogenic carcinoma
lung abscess
Cardiac
bacterial endocarditis
cyanotic heart disease
Gastrointestinal
ulcerative colitis
Crohn's disease
primary biliary cirrhosis
Congenital

Diagnosis The normal nail forms an angle of about 160 degrees with the nailbed. An increase in the angle to 180 degrees or more, is seen early in clubbing when the finger is viewed from the side. In addition, the nailbed feels soft and spongy and there is an increased movement of the nail at the nailbed (*fluctuation*). An objective measurement of clubbing is the ratio of the diameter of the distal phalanx at the nailbed to its diameter at the distal interphalangeal joint (Fig 11.3). Normally this ratio is less than one. A value greater than one suggests clubbing. A drumstick appearance of the distal phalanx is seen in severe clubbing. A classification into doubtful, definite and severe categories has been suggested given the subjectivity in the diagnosis of early clubbing.[1]

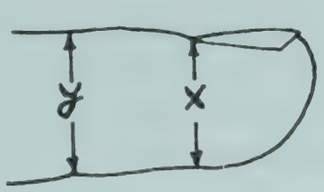


Fig 11.3 Clubbing of fingers is best assessed by determining the ratio of the diameter at the base of the nail (x) to the diameter at the distal interphalangeal joint (y). This ratio is normally less than unity, that is, x/y <1.

Pathogenesis Persistent vasodilation at the tips of the digits is the likely cause of clubbing. In normal individuals an endogenous vasodilator is inactivated by the lungs; if the lungs are diseased or bypassed (as in right to left shunts), the substance is not inactivated and causes persistent vasodilation. Relief of clubbing with vagotomy has also raised the possibility of neurogenically mediated vasodilation. An increase in the number of arteriovenous anastomoses (or *Suquet-Hoyer canals*) in the nailbed had been suggested as a possible mechanism. Such an increase, however, has not been seen at necropsy. Increased clumping of megakaryocytes and platelets with release of platelet-derived growth factors that cause soft tissue overgrowth, has also been suggested as a possible mechanism. Lastly, it has been observed that the presence of finger clubbing in subjects with bronchial carcinoma has correlated with high plasma growth hormone concentrations.

Hypertrophic pulmonary osteoarthropathy sometimes accompanies clubbing and refers to a painful periarticular swelling around the wrist, ankles or elbows, with radiologic evidence of periosteal bone formation (usually in X-rays of the forearm or leg). Gynecomastia may be present in these patients.

[1] Clubbing is said to exist when three experts agree on the diagnosis.

Approach to a Patient with a Solitary Pulmonary Nodule

A solitary pulmonary nodule is defined as a rounded lesion with well-demarcated margins.

Etiopathology Approximately 40 per cent of solitary pulmonary nodules are malignant, and of these the majority are bronchogenic carcinomas. Approximately 40 per cent of these nodules are granulomas, 5 per cent are due to metastatic disease and the rest are due to various other causes (Table 11.5).

Clinical approach Usually history, physical examination and skin tests do not yield useful clues to the etiology of a solitary pulmonary nodule. The usual lack of bronchial

Table 11.5 Causes of a solitary pulmonary nodule

1. Primary lung malignancy
2. Metastases
3. Benign tumours
   - Hamartoma
   - Hemangioma
   - Adenoma
4. Infections
   - Hydatid cyst
   - Fungal granuloma
   - Mycobacterial disease
5. Vascular disease (unusual: pulmonary hemorrhage/infarct)
6. Collagen vascular disease (unusual: Wegener's granulomatosis, rheumatoid arthritis)

communication explains the poor diagnostic yield of sputum cytology in these patients. The most useful clues come from previous and present chest radiographs. Granulomas grow at a rate of 2 mm per year whereas tumours double in 6–8 months. The failure of a lesion to progress in serial X-rays over a two-year period strongly suggests a benign etiology. Concentric or central calcification suggests a benign lesion, a *'popcorn' calcification* suggests a hamartoma. Eccentric calcification, umbilication, satellite lesions and notching of the rib margins suggest a malignancy.

When a lesion is not obviously benign, obtaining a tissue diagnosis by percutaneous transthoracic needle aspiration (for peripheral nodules), fibreoptic bronchoscopy (for nodules > 2 cm in size and within 2 cm of the hilum) or with thoracotomy is essential. In patients over the age of 35, the chances of malignancy are high and the diagnosis is to be vigorously pursued.

Approach to a Patient with Cyanosis

Cyanosis is defined a bluish discolouration of the skin and the mucous membranes. The bluish colour is due to the presence of deoxygenated hemoglobin in the blood traversing the skin and mucosa.

Etiology Cyanosis occurs when there is deoxygenated hemoglobin in excess of 5 g/dl in the blood. Cyanosis usually corresponds to an arterial oxygen saturation of less than 85% and a P_aO_2 less than 7 kPa (53 mmHg). In the presence of severe anemia, cyanosis may not be evident clinically despite hypoxemia and desaturation of blood (because the absolute amount of deoxygenated hemoglobin may be less than 5 g/dl).

Cyanosis may be *peripheral* or *central*. When both the skin and the mucosal surfaces are blue in colour, the patient has central cyanosis. Causes of central cyanosis include arterial

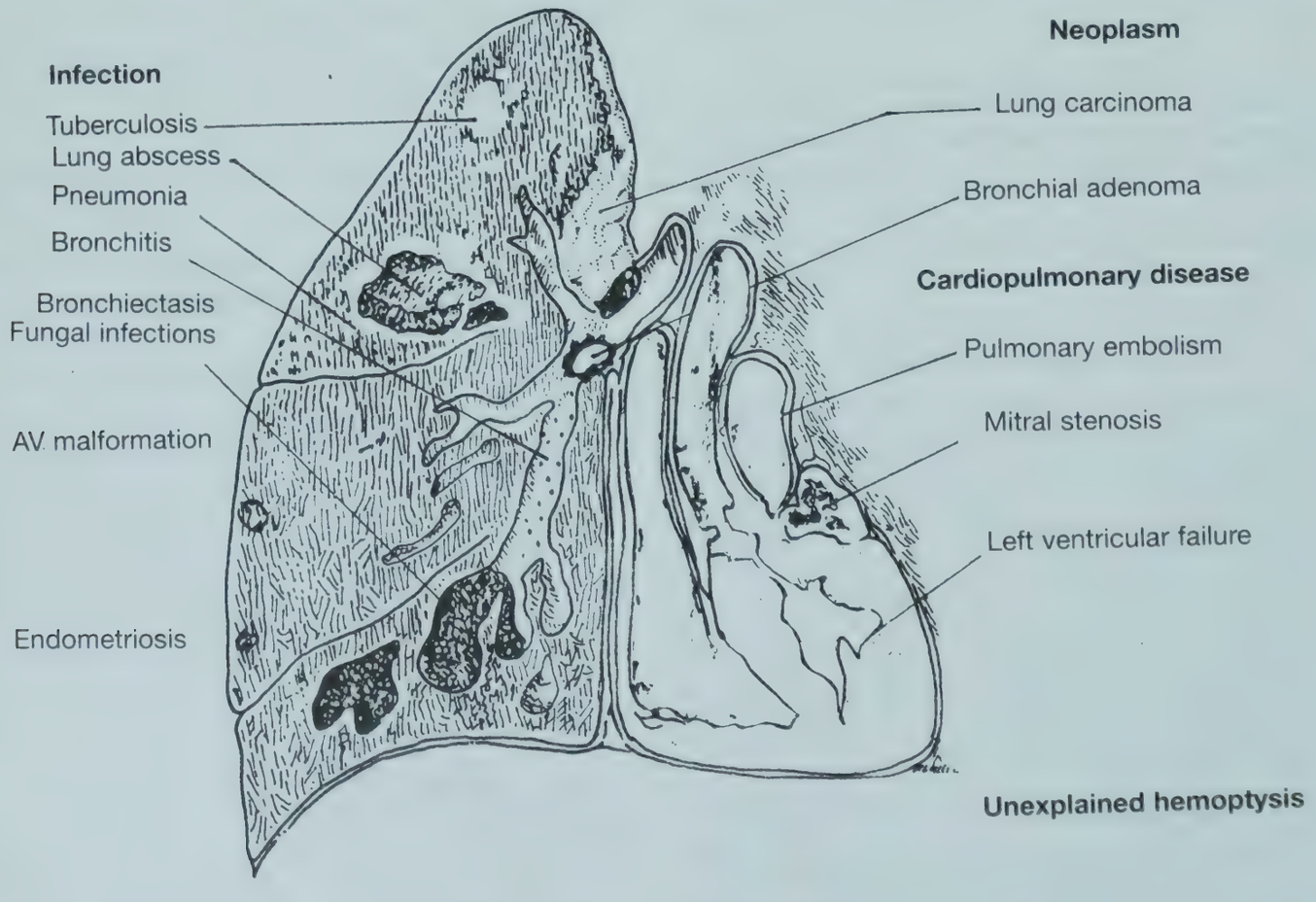


Fig 11.4 Etiology of hemoptysis

hypoxemia due to any cause (severe pulmonary disease with cor pulmonale, V/Q mismatch as in pulmonary thromboembolism), congenital cyanotic heart disease (such as Fallot's tetralogy), polycythemia rubra vera, pulmonary arteriovenous malformation, abnormal vascular channels (such as portal vein–pulmonary venous connections in cirrhotic patients), or abnormal hemoglobins (such as low affinity hemoglobin [hemoglobin Kansas]; sulph- or methemoglobinemia).

In peripheral cyanosis only the skin is blue (typically in the distal part of the extremities), and the mucosa (such as the tongue) retains a normal pink colour. Nonetheless, clinical distinction between the two types of cyanosis may be difficult. Peripheral cyanosis signifies a slow circulation of blood through the tissue microvasculature. This prolonged transit time permits the tissues to extract an excessive amount of oxygen from oxyhemoglobin in the blood. Causes of peripheral cyanosis include shock (due to any cause), venous obstruction, peripheral arterial disease, Raynaud's disease, severe mitral stenosis and tricuspid valve disease (severe systemic venous hypertension with dilatation of the subpapillary plexus of the cutaneous tissues).

Diagnosis When evaluating a patient with cyanosis, the important questions to be asked include the duration of cyanosis (longstanding cyanosis from birth suggests congenital cyanotic heart disease) and a history of drug intake (agents that can cause sulph-/methemoglobinemia). A history of longstanding symptoms suggestive of pulmonary disease may point to a pulmonary cause of cyanosis. Physical examination must include observation of the distribution of cyanosis, assessing the presence or absence of clubbing, auscultation of the cardiovascular system and the chest, and evaluation of the peripheral arterial and venous circulation. The presence of clubbing with cyanosis often denotes a longstanding etiology like cyanotic congenital heart disease. When cyanosis is observed in the lower extremities but not in the upper extremities (*differential cyanosis*), an Eisenmenger syndrome due to reversal of shunt across a patent ductus arteriosus is likely. Presence of a continuous murmur in the chest raises the possibility of a pulmonary arteriovenous malformation. Unilateral cyanosis restricted to one extremity points to a local vascular insufficiency as the possible cause.

Investigation The chest X-ray and the electrocardiogram are useful adjuncts to clinical examination in evaluating a potential cardiac etiology of cyanosis. When presence of an abnormal hemoglobin is suspected as the etiology, a sample of blood in a test tube may be exposed to room air. If the blood does not turn pink and retains a brownish tinge, methemoglobinemia may be suspected and spectrophotometric evaluation may be ordered for confirmation. Disappearance of cyanosis on warming of extremities is seen in Raynaud's disease. Measurement of oxygen saturation (and evaluation of the degree of residual cyanosis) after oxygen inhalation may be used as a measure of the degree of reversibility of cyanosis. Treatment is targeted at the underlying etiology of cyanosis.

Approach to a Patient with Hemoptysis

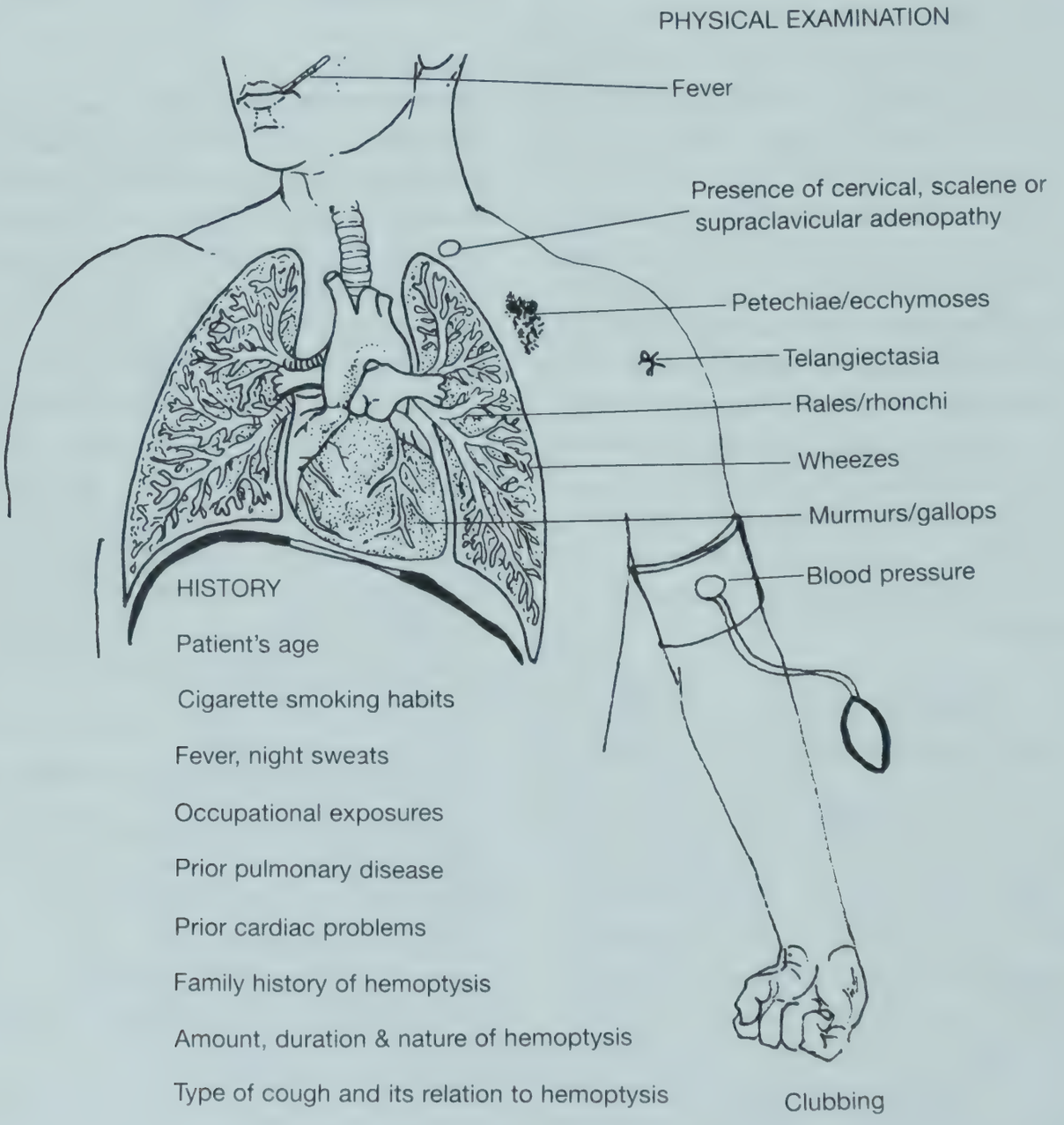
Hemoptysis is the coughing up of either blood-tinged sputum or of frank blood from the respiratory tract below the level of the larynx. Hemoptysis is said to be mild, moderate or severe if the amount of blood loss per 24 hours is 20 ml, 20–200 ml or 200–600 ml, respectively.

Etiology There are several etiologic causes of hemoptysis. The common causes are depicted in Fig 11 4. Tuberculosis, bronchiectasis, lung carcinoma and rheumatic mitral stenosis are among the commonest causes in India. In almost a tenth of cases, hemoptysis remains

unexplained (*cryptogenic*) despite extensive investigation. It has been suggested that such cases reflect undetectable minor inflammatory bronchitis.

Pathophysiology The source of blood in hemoptysis may be pulmonary arteries, pulmonary veins or capillaries, bronchial veins or arteries, or vascularised mucosa. The pulmonary arterial system is a low pressure system whereas the bronchial arterial system is a high pressure system; hemorrhage from the bronchial vascular system, therefore, tends to be brisk, more severe and can be exsanguinating.

Bronchial vessel bleeding is seen in bronchiectasis (with proliferation of the bronchial circulation), in neoplasms (increased bronchial arterial flow in lung carcinoma with secondary necrosis of tumour tissue or of vascularised mucosa) or in mitral stenosis (rupture of distended bronchial veins or bronchopulmonary venous connections).



Important : Hemoptysis must initially be differentiated from other possible sites of bleeding, that is, gastrointestinal, oral, nasopharyngeal and laryngeal.

Fig 11.5 History and physical examination in a patient with hemoptysis

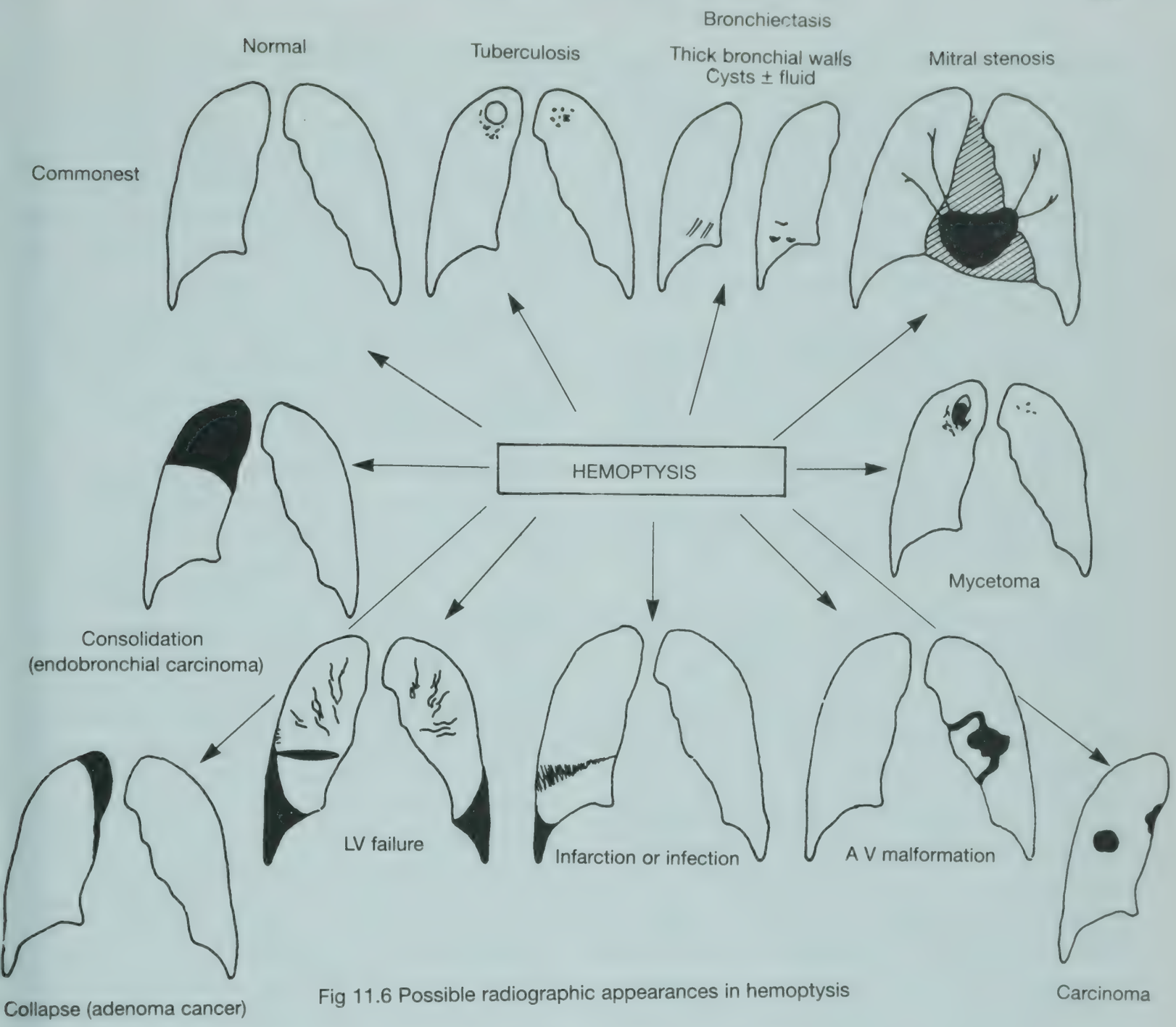


Fig 11.6 Possible radiographic appearances in hemoptysis

A pulmonary vascular source of bleeding is seen in pulmonary embolism (usually with associated infarction), left ventricular failure (as in rupture of the small pulmonary veins and capillaries) or pulmonary vasculitis.

The two major consequences of a significant episode of hemoptysis are the risk of *exsanguination* (hypovolemia and its sequelae) and the risk of *asphyxiation* (hypoxemia due to flooding of the airways and the contralateral lung).

History and physical examination The clinician must firstly differentiate hemoptysis from bleeding from other sites, such as gastrointestinal, oral or nasopharyngeal sources. The patient's age, smoking habits and the presence of chest symptoms help in establishing an etiologic diagnosis. Below the age of 45 years, tuberculosis, chronic bronchitis, bronchiectasis and mitral stenosis predominate as possible etiologic causes. Above this age, especially in subjects with a history of chronic cigarette smoking, pulmonary neoplasm becomes a more common cause of hemoptysis. A history of fever suggests pulmonary parenchymal infection. Prior cardiac disease or

cardiac symptoms should alert the clinician to underlying rheumatic valvular heart disease. A history of a coagulopathy or the use of anti-coagulant drugs must also be sought. A family history of hemoptysis, presence of cyanosis and a history of bleeding from other sites (epistaxis) should raise the suspicion of hereditary hemorrhagic telangiectasia with arteriovenous malformations.

The amount of hemoptysis or nature (that is, blood tinged or frank blood) does not permit a distinction to be made among the various etiologic causes. This information is however vital for instituting appropriate diagnostic workup and treatment.

Physical examination for possible clues to an etiologic diagnosis is shown in Fig 11.5.

Investigations Chest X-rays help in establishing both the possible site of bleeding and on occasion the etiology of hemoptysis (Fig 11.6). Thus a localised infiltrate may suggest an underlying pneumonitis or aspirated blood; a region of atelectasis with oligemia may indicate underlying pulmonary embolism with infarction; a cavity may suggest tuberculosis, lung abscess or a fungal infection, and a central or peripheral mass lesion may suggest a neoplasm. Thickened bronchial walls (*ring shadows*) are seen in bronchiectasis and airways disease whereas an enlarged left atrium along with pulmonary venous hypertension may be seen in rheumatic mitral stenosis.

Bronchoscopy is not required either when there is strong radiological or clinical evidence of non-neoplastic pulmonary disease or when the patient's condition is extremely compromised so that no subsequent action is likely to be taken based on the bronchoscopic findings. Presence of a normal chest X-ray and a history of moderate or severe hemoptysis, especially in a middle aged smoker, is an indication for bronchoscopy to exclude a malignancy. An abnormal chest X-ray in this situation too is an indication for bronchoscopy to biopsy suspicious areas and for obtaining brushings and lavage samples for cytology and appropriate cultures.

Patients with massive hemoptysis may require urgent bronchoscopy (preferably with a rigid bronchoscope) for localising the site of bleeding, aspirating blood and providing both an airway and ventilation. If bronchoscopy fails to identify the site of bleeding, selective bronchial arteriography[1] can be contemplated. Isotope lung scans can also be obtained as an alternative (using technetium^{99m} labelled red blood cells) to localise the sites of bleeding where the tracer will extravasate into the respiratory tree.

Management The immediate goals of therapy are to prevent asphyxiation and to stop the bleeding. The underlying cause of hemoptysis must also be treated, though this is less urgent.

The patient is hospitalised if the hemoptysis is moderate or more. Bedrest in the lateral decubitus position with the bleeding side down and the head tilted down, will prevent aspiration into the non-bleeding lung. Cough suppression with linctus codeine is advisable, taking care to avoid oversedation. Oxygen therapy is indicated if there is evidence of hypoxemia, and volume deficits are corrected. Massive ongoing hemoptysis may require immediate protection of airway by endotracheal intubation and mechanical ventilation when indicated.

Rarely, surgery (pulmonary wedge resection or lobectomy) may be required in patients with life-threatening recurrent massive hemoptysis. Alternative measures that have been utilised include endobronchial tamponade of bleeding sites using balloon-tipped catheters, topical application of thrombin at bleeding sites, laser photocoagulation of bleeding sites and bronchial arterial embolisation. The latter procedure has limited long term success due to the possibility of vessel recanalisation or due to growth of collateral vessels.

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[1] Since spinal arteries communicate with bronchial arteries through the intercostal trunks in 5 per cent of patients, myelitis due to the effect of the contrast medium on the spinal arterial circulation is a rare complication of the procedure.

KEY CONCEPTS

Dyspnea

- Important causes of *acute dyspnea* include pulmonary edema, exacerbation of bronchial asthma or COPD, hysterical hyperventilation, severe pneumonia, pneumothorax and an episode of pulmonary embolism. Causes of *chronic dyspnea* include chronic congestive heart failure (valve disease, myocardial disease), COPD and pulmonary parenchymal disease (interstitial fibrosis).
- *Cardiac asthma* (pulmonary edema) must be distinguished from *bronchial asthma*. The occurrence of dyspnea in an elderly subject who does not have a history of prior asthma, eliciting a previous history of cardiac disease (episode of orthopnea or paroxysmal nocturnal dyspnea), the presence of pulsus alternans, associated diaphoresis, the bubbly nature of the airway sounds and the presence of cyanosis favour a diagnosis of cardiac asthma.
- Non-cardiogenic pulmonary edema (ARDS) may be identified by the presence of an inciting stimulus that causes pulmonary injury and by the absence of any cardiac dysfunction.
- Important investigations for evaluating a patient with chronic dyspnea include a chest X-ray (cardiac enlargement in heart failure; parenchymal infiltrate in pneumonia), an electrocardiogram (evidence of prior myocardial infarction or ventricular hypertrophy), pulmonary function tests (evidence of obstructive or restrictive pulmonary disease) and echocardiography (evaluation of ventricular systolic function and valvular heart disease).

Finger clubbing

- Finger clubbing may be due to congenital cyanotic cardiac disease or due to pulmonary suppuration (lung abscess, bronchiectasis), infiltration (interstitial fibrosis) or neoplasms.
- Fluctuation of the nailbed, a 'beaked' appearance and changes in nail capillary beds are associated with the presence of finger clubbing.
- Clubbing is not a feature of uncomplicated pulmonary tuberculosis or COPD.

Solitary pulmonary nodule

- About 40% of solitary pulmonary nodules are malignant while another 40% represent granulomas.
- Examination of the roentgenographic characteristics of the nodule and its growth on serial X-ray films (if available) yields important clues to its etiology. An absence of changeover time or a slow progression (long doubling time), and the presence of *concentric* calcification are clues to the benign nature of the nodule. *Popcorn* calcification suggests a granuloma. The presence of *eccentric* calcification, *spiculation,* or umbilication favours a malignant nature of the nodule.

Cyanosis

- Cyanosis may be *peripheral* or *central*. Peripheral cyanosis is due to a prolonged blood transit time or to circulatory stasis. It is evident only on the skin of the extremities and in the peripheral nailbeds. Causes include cold exposure, shock and arterial or venous obstruction. Peripheral cyanosis is reversed on rewarming of extremities.
- Central cyanosis may be due to an intracardiac right to left shunt, a pulmonary arteriovenous fistula, hemoglobinopathies, or due to severe pulmonary disease. Central cyanosis is evident on the mucosal surface and the skin; it is usually discernible when the arterial oxygen saturation is <85%.
- Investigations include the measurement of arterial oxygen saturation (breathing room air and while inhaling 100% oxygen) and hemoglobin spectroscopy (when a hemoglobinopathy is suspected).

Hemoptysis

- An episode of hemoptysis must be distinguished from *hematemesis*. In hemoptysis, the blood is coughed up, is bright red in colour and has a frothy appearance. In hematemesis, the blood is vomited, there is usually some abdominal discomfort and the vomitus is dark red in colour.
- Common causes of hemoptysis include tuberculosis, mitral stenosis, bronchiectasis, bronchogenic, carcinoma and chronic bronchitis (usually streaking alone in the latter condition).
- A careful history and a meticulous physical examination often provide valuable clues to the etiology of hemoptysis. A chest X-ray may provide additional confirmatory evidence: *mitralisation* of the heart (straight left border, enlarged left atrial appendage, prominent pulmonary artery segment and pulmonary venous hypertension) in mitral stenosis, *apical infiltrate* in TB, *ring shadows* in bronchiectasis or a *mass* lesion in lung cancer.
- If there is no evidence of active pulmonary bleeding at the time of evaluation, the patient may be investigated by obtaining a sputum cytology, bacteriologic staining of sputum and fibreoptic bronchoscopy. A ventilation-perfusion scan may be obtained if pulmonary embolism is suspected. Investigations may not yield any clue in a significant proportion of patients (*cryptogenic hemoptysis*).
- If there is active pulmonary bleeding, the initial objectives are to prevent exsanguination (volume loss) and asphyxiation (due to flooding of the contralateral lung). Volume replacement is immediately initiated. The availability of suctioning and intubation equipment by the bedside is mandatory. Bedrest, sedation and cough suppressants are useful adjuncts. Rigid bronchoscopy is preferable for identifying the bleeding site if the bleeding is profuse and continuous.
- Management is also guided by the underlying etiology; diuretics help to lower pulmonary capillary and venous pressures in mitral stenosis, antibiotics (and anti-tubercular drugs for tuberculosis) are indicated if there is evidence of parenchymal pulmonary infection.

11.3 Diagnostic methods in pulmonary medicine

Sputum Examination

Abnormal bronchial secretions produced due to tracheobronchial or pulmonary inflammation are expectorated as sputum. An early morning specimen of sputum is usually convenient to obtain, as abnormal bronchial secretions tend to accumulate overnight. The sputum is collected in a sterile container known as a *sputum cup.*[1] If the patient has no expectoration and a sputum examination is required, for instance for cytologic examination, inhalation of an ultrasonically generated mist of saline solution (or of heated nebulised hypertonic saline mixed with propylene glycol) may be used to provoke a cough. In case it is likely that the patient is swallowing his sputum, a good alternative is to aspirate the gastric contents early in the morning before the patient brushes his teeth. Three such successive aspirates have been shown to have a high diagnostic yield for the diagnosis of pulmonary tuberculosis. Since non-pathogenic mycobacteria can be found in the gastric contents, a proof by the culture of Mycobacterium tuberculosis is required.

The gross examination of sputum can convey some information. The amount, colour, consistency, smell and the presence or absence of blood is noted. Patients with bronchiectasis and lung abscess usually expectorate more than 20 ml of sputum in a day. Expectoration of more than 100 ml of sputum in a day is called *bronchorrhea*; it is seen characteristically in association with alveolar cell carcinoma but also occurs sometimes in asthma and chronic bronchitis. Yellow or green coloured sputum[2] usually suggests infection but on occasion patients with chronic bronchitis produce yellow sputum in the mornings and mucoid sputum in the evenings. Foul-smelling sputum usually indicates an infection by anerobes. The sputum may contain yellow white particles (*Dittrich's plugs*) that represent inspissated secretions containing disintegrated fatty acids, in patients with bronchiectasis. Calcified particles (*broncholiths*) may be present in the sputum and originate from calcified tuberculous lymph nodes, silicotic nodules, parenchymal histoplasmosis lesions or the rare condition of idiopathic broncholithiasis. Black sputum (*melanoptysis*) may be seen in coal workers' pneumoconiosis.

Initially a wet mount of the viscid part of the sputum should be screened with the diaphragm of the condenser of the microscope coned down to produce a semi-dark field effect. The presence of >25 leucocytes/low power field and <10 squamous cells/low power field suggests a deep respiratory sample. The leucocytes are then examined with an oil immersion lens. Neutrophils are trilobed and have small granules with margins blurred due to brownian motion whereas eosinophils are bilobed and have refractile, non-mobile granules. The sputum of

[1] Usually contains carbowax which prevents cellular degeneration

[2] The green colour is due to liberation of the enzyme myeloperoxidase from broken-down leucocytes.

asthmatic patients may contain more than 20 per cent eosinophils. Pointed rhomboid crystals (*Charcot-Leyden* crystals), fine spirals of mucous forming bronchiolar casts (*Curschmann's spirals*) and clumps of ciliated epithelial cells (*Creola bodies*) may be found in the sputum of asthmatics. Abundant neutrophils in sputum indicate infection. Fungal hyphae can also be seen on occasion (sputum is mixed with 10% KOH before smear preparation).

A Gram stain of the sputum may provide valuable information and help in antibiotic selection for treatment, pending the availability of sputum culture reports; they correlate fairly well. A Ziehl Nielsen smear can be made, after concentrating the sputum, to look for acid-fast bacilli. If available, the fluorescent rhodamine auramine stain of sputum may also enable a rapid detection of mycobacteria. On occasion, asbestos bodies (10–180 μ in size) which are elongated structures with bulbous ends, may be seen. They stain blue with potassium ferrocyanide.

Cytologic examination of the sputum stained with Papanicolaou stain by a trained person can help detect malignant cells, exfoliated into the bronchial tree. The sensitivity varies from 60–85 per cent, being higher for central and lower lobe tumours, and for squamous and small cell cancers (which are also more central).

Chest Roentgenogram

The chest X-ray is a fundamental investigation in any suspected pulmonary or mediastinal disease. An orderly approach towards analysing the chest radiograph is therefore essential. Knowledge of what is 'normal' is also important before deciding that the chest roentgenogram is 'abnormal'.

Reading a chest X-ray

The marker on the chest radiograph identifies the right or the left side; this is important for the identification of malpositions such as dextrocardia (heart on the right side of chest) or situs inversus. The gastric bubble is normally seen below the left hemidiaphragm in an erect film. In anteroposterior films (AP), scapulae are projected in part over the lung fields whereas in posteroanterior radiographs (PA), the scapulae are positioned off the lungs lying posterolaterally. PA[1] films do not cause geometric magnification of the anteriorly positioned heart and are hence preferred over AP films. Erect films,identified by a gastric bubble that has risen to the fundus of the stomach under the left hemidiaphragm, are preferred to supine films as in the former pulmonary and pleural pathology is better seen (lungs are more expanded) as are air fluid levels. A gravitational gradient in vessel size (that is, from larger size at base to a smaller size at the apex) present in the normal erect film also helps in diagnosis when it is absent or altered. Chest radiographs can be taken with X-rays of varying penetrating ability, high (140–150) or low (60–80) kV. High kV films detect lung lesions and mediastinal pathology more easily, but have the disadvantage that calcific and ossified structures become less obvious and therefore more difficult to assess.

While reading a chest radiograph one must check the symmetry of the medial ends of the clavicle to assess the extent of rotation of the patient, if any. Rotation of the patient can distort the hila and mediastinum.

Normal and abnormal chest X-rays

The lung fields occupy the major portion of the radiograph. Vessels are the only structures seen in the lung apart from an occasional end-on airway. Vessels decrease progressively in size from the hilum to the periphery, disappearing about 1 cm from the chest wall. Upper zone vessels are thinner than lower zone ones; reversal of this pattern (*cephalisation*) or equalisation of this relationship occurs at low lung volumes, in conditions with raised pulmonary venous pressures or basal lung

[1] PA indicates that the X-ray beam passes from the posterior to the anterior.

pathology. A hairline width minor horizontal fissure can be seen in the normal PA radiograph extending from 1 cm below the right hilum to the chest wall; displacement indicates some sort of volume change and a further thickening may indicate pleural fluid.

The hemidiaphragms in the normal chest radiograph appear highest medially with a smooth curve to an acute costophrenic angle laterally, the right hemidiaphragm being higher than the left by upto 3 cm. The right hemidiaphragm may exhibit one or more humps as a normal variation. Whenever the diaphragm peaks laterally with a straight medial segment and a blunt costophrenic angle, a subpulmonic effusion mimicking a raised hemidiaphragm must be suspected.[1]

The trachea is seen in the normal PA film as a transradiant band midway between the clavicular heads. The right wall of the trachea is seen as a translucent paratracheal line — its absence is an important sign of paratracheal adenopathy. The azygos vein is seen as a soft tissue density in the right tracheobronchial angle and is enlarged whenever central venous pressure or portal venous pressure is elevated.

The hila consist mainly of vascular structures, though nodes may contribute in pathologic states. The left hilum is 1–2 cm higher than the right hilum and appears more foreshortened. Displacement of either hilum is an important evidence of differential volume changes in the suprahilar and infrahilar parts of the ipsilateral lung. The right basal pulmonary artery is clearly seen at the right hilum; it is abnormal for the diameter of this vessel to be more than 16 mm and this is usually indicative of pulmonary arterial hypertension. In such conditions the pulmonary vasculature too is pruned towards the periphery (prominent central hilar vessels with distal cut off). Hilar enlargement could also be due to lymph node enlargement.

Unilateral hilar adenopathy is seen in pulmonary tuberculosis, fungal diseases, tularemia and psittacosis. Bihilar adenopathy is seen in sarcoidosis and lymphomas.

Pulmonary opacities

Lung lesions produce several abnormal patterns of opacities.

1. A *consolidation* reflects the replacement of air in the alveoli by fluid (transudate in pulmonary edema, exudate in pneumonia, and blood in infarction or contusion) or by tissue (alveolar cell carcinoma, lymphoma). The process spreads through the pores of Kohn giving rise to an opacity of variable shape and with ill-defined edges. Patent airways which pass through a consolidated lung appear as dark branching transradiant linear structures — the air bronchogram; this important sign differentiates a consolidation from other opacities such as a pleural effusion or a collapse. In a lobar consolidation the organisms damage the terminal airspaces throughout a lobe. The infection spreads throughout a lobe respecting pleural boundaries. In a lobular[2] consolidation (bronchopneumonia) the infective organisms damage the walls of the terminal and respiratory bronchioles and infection spreads along the intralobular airway until the pulmonary lobule is partially or totally involved. The process tends to respect the septal boundaries so that a poorly defined fluffy or patchy opacity results.

2. *Interstitial shadows* result when the infective organisms damage the bronchiolar walls, peribronchial tissues and interlobular septa. Linear, reticular and small nodular opacities are typically seen. Interlobular septa may be prominent when they are infiltrated (as in case of pneumoconiosis, lymphangitic carcinomatosa, hemosiderosis) or water logged (as in pulmonary venous hypertension).

The septal lines are horizontal, short lines usually 1–2 cm long and 1–2 mm thick, visible

[1] Other causes of a raised hemidiaphragm include phrenic nerve palsy, diaphragmatic eventration or hernia.

[2] A secondary pulmonary lobule consists of 3–5 terminal bronchi and acini.

especially at the costophrenic angles (known as the Kerley B lines).

3. *Collapse* of a part of the pulmonary parenchyma also leads to a pulmonary opacity. Such a collapse may result from airway obstruction (obstructive collapse), lung compression (compressive collapse), lung stiffening (secondary to a fibrotic process) or due to an increase in adhesive forces (such as the loss of surfactant in pulmonary embolism). There are two cardinal features of a lobar collapse: i) an opacity with its apex at the hilum is present, and ii) there is an accompanying volume loss manifested by elevation of the ipsilateral hemidiaphragm, mediastinal shift, hilar shift and crowding of ribs. However, mild collapse of a lung lobe may not manifest as either. It may be manifest by just vessel crowding and fissural shifting. Collapse of the middle lobe and the left lower lobe are especially likely to be missed. The collapse of the middle lobe may be seen only as a lack of clarity of the right heart border (*silhouette sign*). Left lower lobe collapse is missed because it hides behind the heart. A careful assessment of the relative right and left heart density, the contour of the diaphragm and the descending aorta, and the position of the left hilum may help in the diagnosis.

4. *Pulmonary nodules* are spherical opacities that may be solitary or multiple. The differential diagnosis of a solitary pulmonary nodule has been discussed in Chapter 11.2. Multiple nodules may be medium sized (9–10 mm) or miliary (1–2 mm).

The causes of multiple nodules are listed in Table 11.6.

5. *Ring opacities or cavities* (Fig 11.7) are annular in shape and have a transradiant centre. When they are larger than 1 cm and have thin walls (<1 mm), they are referred to as cysts. Pulmonary cysts may represent bullae, bronchogenic cysts, bronchiectatic cysts, hydatid cysts or pneumatocoeles. Lesions with thicker walls are called cavities. Nearly all large nodules may cavitate, though some do so more often than others depending on the etiologic cause. Cavitation in a consolidation is seen in tuberculosis, staphylococcal infection and necrotising infection (gram-negative organisms and anerobes). Other less common causes of pulmonary cavities include Wegener's granulomatosis, cavitary tumours and cavitary infarction.

Pleural effusion

The earliest roentgenologic sign of collection of pleural fluid is blunting of the posterior costophrenic angle on a lateral chest radiograph, this being the most dependent part of the pleural space. Moderate effusions blunt the lateral costophrenic angles on a PA chest film. Large pleural effusions may render the hemithorax

Table 11.6 Etiologic causes of multiple pulmonary nodules

Medium sized	Miliary
1. Mid/Upper zone predominance	1. Calcific density
Silicosis	Alveolar microlithiasis
Sarcoidosis	Siderosis
Eosinophilic granulomatosis	Stannosis
2. Any lung zone	2. Soft tissue density
Metastases	Coal workers' pneumoconiosis
Tuberculosis	Tuberculosis
Varicella	Fungal infection
Abscesses	Extrinsic allergic alveolitis
Arteriovenous malformations	Hemosiderosis

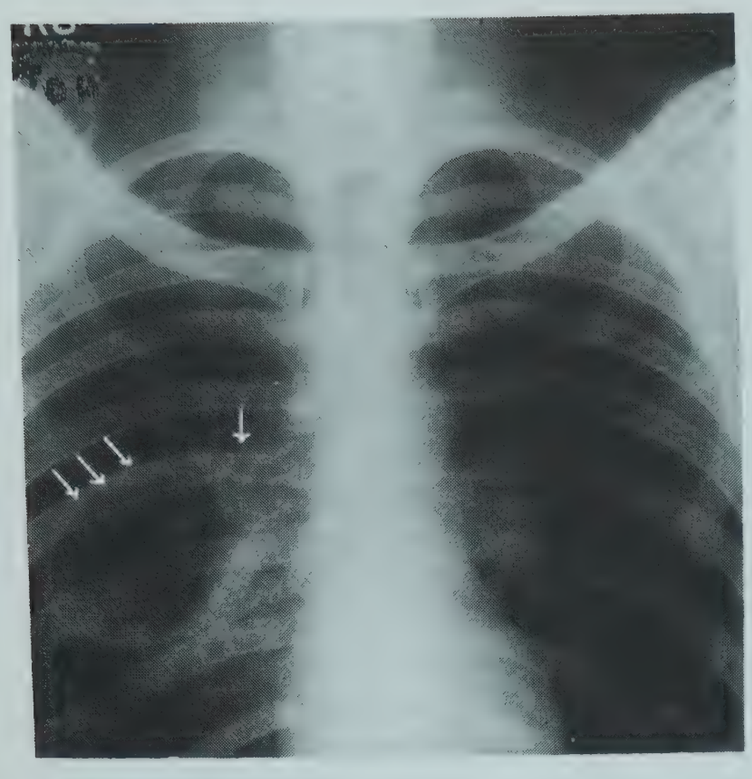


Fig 11.7 Plain X-ray of chest (AP view) of a 25-year old man with fever and a chronic cough. There is a large thin-walled cavity (multiple arrows) and a smaller cavity (single arrow) adjoining it. This patient had infection with atypical mycobacteria.

opaque. Blunting of the costophrenic angles may also be due to pleural thickening. Differentiation of the two, that is, fluid versus thickening, can be made either with a *lateral decubitus film* (when fluid layers out) or with an ultrasound examination. Sometimes pleural fluid may collect selectively under the lung; such a collection is called a subpulmonic effusion and may mimic a raised hemidiaphragm. An effusion may be suspected if the diaphragm peaks in its lateral third with a straight medial segment, especially if there is associated blunting of costophrenic angles.

Pleural calcification

The pleura may be calcified in asbestosis, in a previous hemothorax or in an empyema (especially post-tubercular).

Transradiancy

A reduction in radiographic density of the lungs is called transradiancy or hypertranslucency. When localised and unilateral, transradiancy may be seen in bullae, emphysema, pulmonary embolism and developmental failure (*Macleod syndrome*).

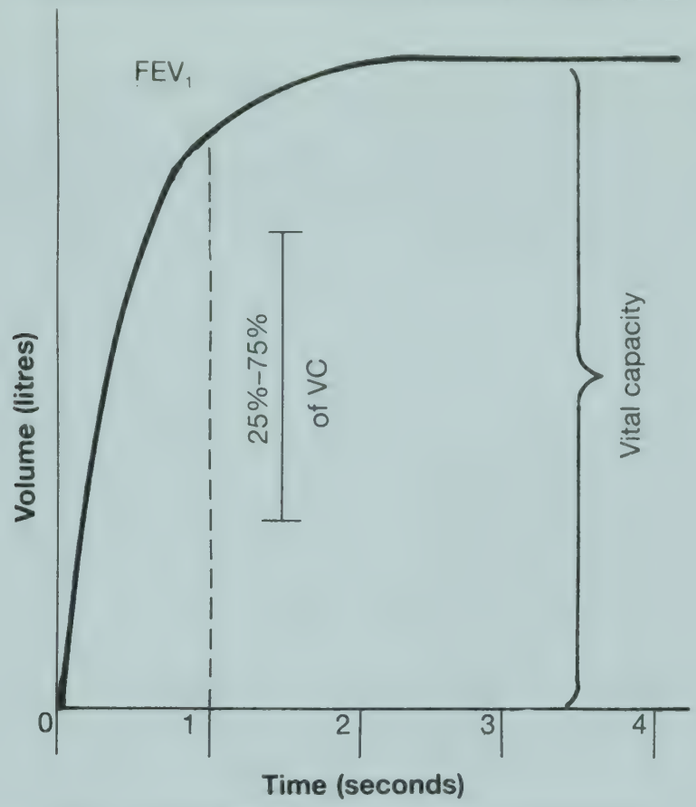
Pulmonary Function Tests

Pulmonary function tests are tests that objectively measure the ability of the lungs to ventilate and carry out gas exchange. Thus these tests include: 1) tests of airway function; 2) tests of pulmonary volume; 3) tests of gas exchange; 4) tests of respiratory muscle function; 5) tests of ventilatory control mechanisms; and 6) tests of exercise performance.

Indications Pulmonary function tests are indicated for

1) establishing or excluding a respiratory cause of dyspnea; 2) diagnosis of obstructive airways disease and localising the site of obstruction; 3) prognostic purposes, to monitor progression of a lung disease or the patient's response to treatment (for example in interstitial lung disease); 4) evaluation of pulmonary involvement in systemic disease (scleroderma) or pulmonary side effects of drugs such as amiodarone; 5) preoperative evaluation of heavy smokers or obese elderly individuals or subjects with preexisting lung diseases being considered for thoracic or upper abdominal surgery; 6) epidemiologic observations; and 7) evaluation of exercise performance. However, the likelihood of obtaining useful information is remote in young asymptomatic non-smokers with normal chest roentgenograms. These function tests are not a substitute for a thorough evaluation of the patient by both physical examination and elicitation of history.

Principles All pulmonary function tests measure either displaced volume (with a spirometer) or air velocity (with an anemometer or a mass flow meter). These tests are subject to diurnal variation, airway resistance being highest in the morning, and variation due to differences in posture and mood. Occasionally, large spontaneous variations have been noted in



FEV_1 = forced expiratory volume in first second

VC = vital capacity

Fig 11.8 Volume-time relations showing FEV_1 and vital capacity

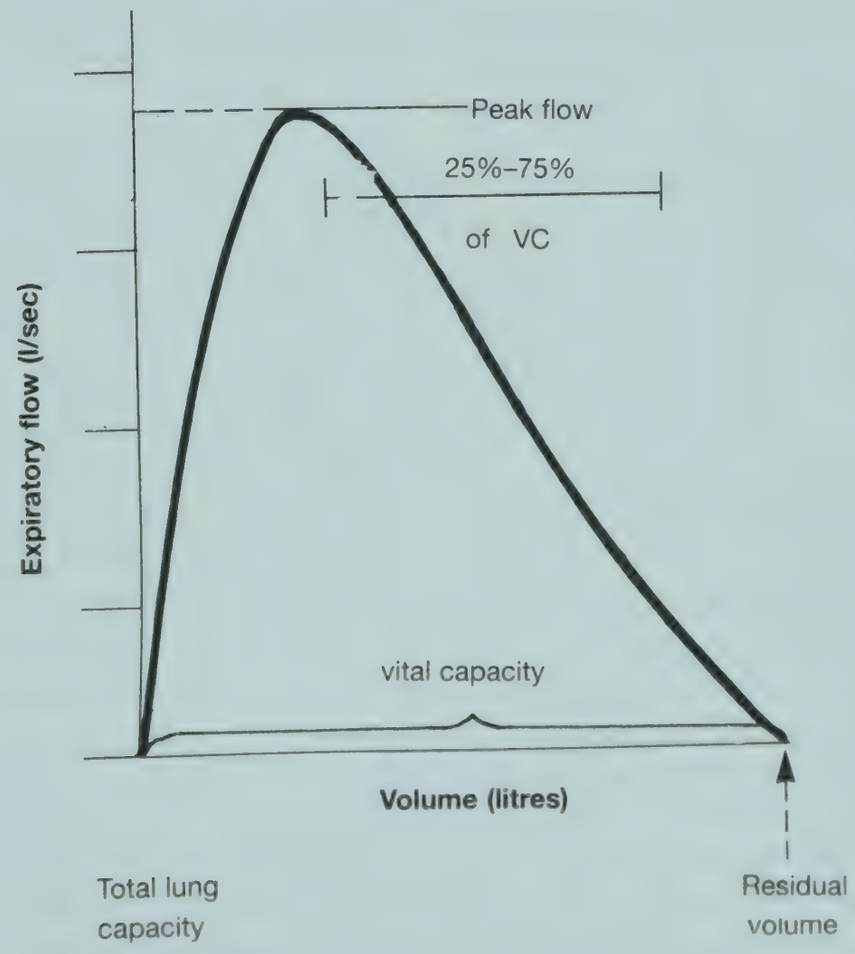


Fig 11.9 Flow-volume relations showing vital capacity and maximal expiratory flow

normal subjects. Prior smoking, exposure to cold air or recent chest infection can influence pulmonary function tests. All values are expressed at BTPS conditions (body temperature, ambient barometric pressure and saturation).

Tests of airway function

Peak expiratory flow (PEF) is the most widely used test and measures the maximum expiratory flow rate over the first 10 milliseconds of an expiration. PEF is dependent on the subject taking the maximum possible breath in and then blowing out hard, that is, it is effort-dependent. It is reduced in diseases of airway obstruction and expiratory muscle weakness. *Forced expiratory volume* represents the integrated flow over the first second of expiration (normal value being 70–80 per cent) and is relatively effort-independent. In any cause of airway obstruction, FEV_1, is reduced more than the forced vital capacity (FVC), so that the ratio of FEV_1/FVC is reduced to below 65 per cent. In restrictive lung disease both FEV_1 and FVC are reduced proportionately, so that the ratio FEV_1/VC is preserved. Maximum midexpiratory flow rate (MMEFR or FEV_{25-75}) is the average expiratory flow during the middle half of the forced vital capacity. It is more variable than FEV_1 but a more sensitive index of flow limitation in small airways. The above three tests utilise a graphic representation of flow plotted against time (Fig 11.8).

The recording during spirometry of expiratory flow plotted against volume produces a triangular shaped loop (Fig 11.9).

There is an initial peak (PEF) followed by a decline to zero at the *residual volume* (RV). An inspiratory loop is obtained by having the patient breathe from the residual volume back to *total lung capacity* (TLC). In asthma and chronic bronchitis, there is sustained systematic reduction in flow rate of the expiratory loop throughout the vital capacity due to a reduction imposed on the flow by narrowed airways. This is known as *volume-dependent airway collapse.* In emphysema, the airways collapse due to a reduced lung elasticity with a dramatic reduction in airflow (*pressure-dependent airway collapse).*

The flow volume curve also provides information about flow rates towards the end of expiration which is at $\dot{V}50$ (at 50% of FVC) and at $\dot{V}$ 25 (last 25% of FVC). In early small airway disease the only abnormality is reduced flows at $\dot{V}25$ and $\dot{V}50$, while FEV_1 and PEF may be normal. Similarly the flow volume curves when breathing room air can be compared with similar curves obtained when breathing a mixture of 80 per cent helium and 20 per cent oxygen to investigate small airway disease. Flow in large airways is turbulent and dependent on gas density whereas flow in small airways is laminar and independent of gas density. Therefore, with small airway disease, the two curves become identical at a higher volume whereas in large airway disease the flow improves with the less dense helium-oxygen mixture and the two curves become identical at a smaller volume.

The flow volume loop is also useful for localising the site of upper airway obstruction, whether intrathoracic or extrathoracic, and for indicating whether it is fixed or variable, that is, allowing the tracheal wall to move during inspiration and expiration. A fixed obstruction (such as, goitre or lymph node) reduces both inspiratory and expiratory loops (Fig 11.10), whereas a variable extrathoracic obstruction (such as vocal cord paralysis) produces a greater reduction in the inspiratory flow loop due to an inspiratory drop in airway pressure. If, however, the obstruction is intrathoracic, inspiration generates a negative, intrathoracic pressure with a resultant widening of the airway; flow reduction is therefore greater in expiration. If a flow volume curve is not available, the ratio between PEF (l/min) / FEV_1 (ml) provides a clue to upper airway obstruction. Normally this ratio is greater than 10; a ratio less than 10 suggests upper airway obstruction.

Table 11.7 Pulmonary function findings in common lung disorders

Test	*Asthma*	*COAD*	*Restrictive lung disease*
FEV_1	↓↓	↓↓	↓
FVC	↓	↓	↓↓
FEV_1/FVC%	↓	↓	N or ↑
RV	↑	↑	↓
TLC	N or ↑	N or ↑	↓
DL_{CO}	N or ↑	↓	N or ↓
Bronchial Provocation	↑↑	N or slight ↑	Unhelpful

N: Normal ↑ Increased ↓ decreased DL_{CO}: Diffusion capacity for carbon monoxide

COAD : chronic obstructive airway disease

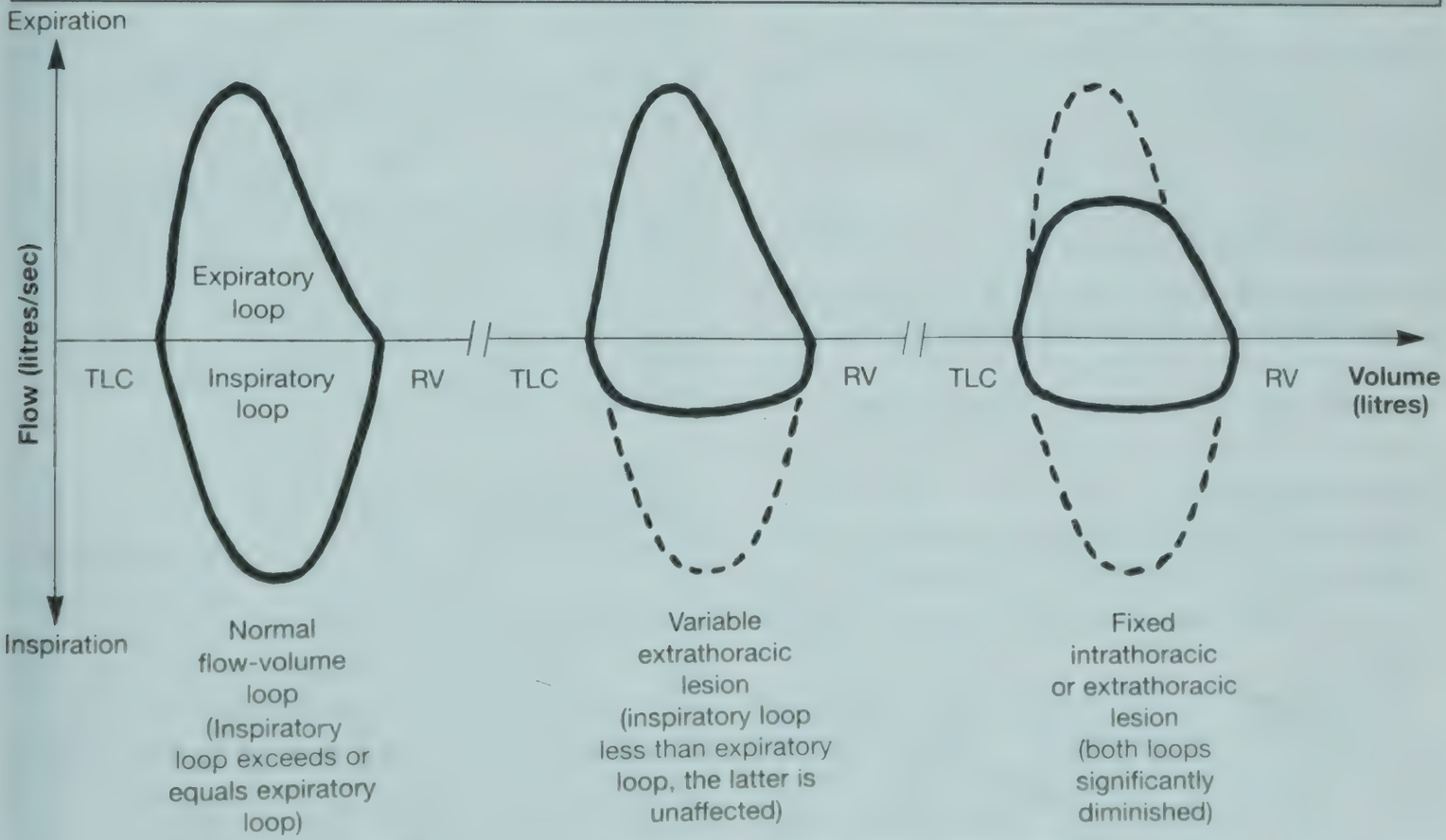
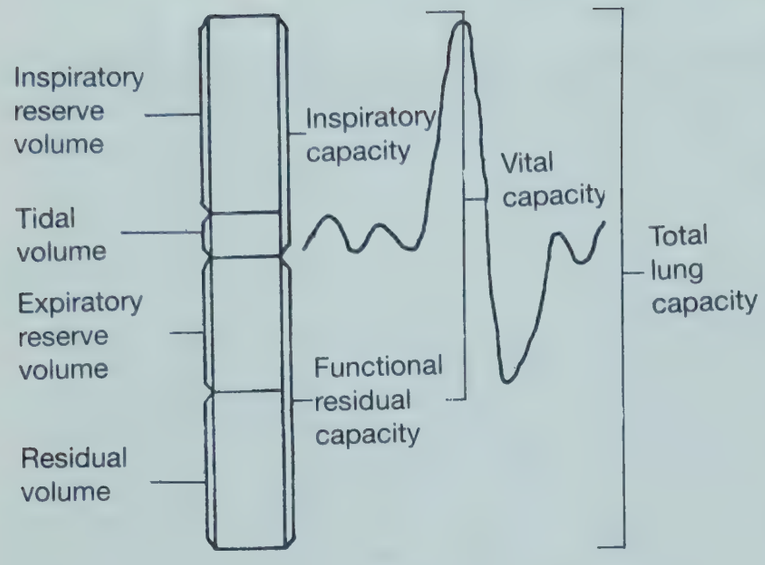


Fig 11.10 Detection of the site of upper airway obstruction
TLC = total lung capacity; RV = residual volume



Tidal volume - Volume of air inspired and expired with each normal breath

Vital capacity - Volume of air expelled by maximal expiration after a maximal inspiration

Residual volume - Volume of air remaining in lungs after completion of the most forceful expiration

Inspiratory reserve volume - Volume of air that can be inspired in excess of tidal volume

Expiratory reserve volume - Volume of air that can be expired after end of a normal tidal expiration

Inspiratory capacity - Volume of air taken in by maximal inspiration after a normal expiration

Functional residual capacity - Volume of air remaining in lungs after a normal expiration

Total lung capacity - Maximal volume to which lungs can be expanded by the maximal inspiratory effort

Fig 11.11 Definitions of pulmonary volumes

Test of lung volume

Measurement of lung volume provides valuable diagnostic and functional information. The various subdivisions of lung volume are defined in Fig 11.11.

Vital capacity (VC) and its subdivisions are measured with a spirometer. Measurement of total lung capacity (TLC) and residual volume (RV) require indirect methods such as *gas dilution technique* or *plethysmography.* In the gas dilution technique a known concentration of helium is breathed in a closed circuit and allowed to equilibrate with the gas already present in the lung. The change in the concentration of gas allows calculation of the lung volume at which the inert gas was inspired. Total lung capacity depends on the balance between the inspiratory muscles that expand the chest and the tendency of the lungs and chest wall to recoil inwards. Residual volume is determined by the balance between the expiratory muscles and the tendency of the thorax to recoil outwards at low lung volumes.

Airway disease increases residual volume; the RV/TLC % is a sensitive measure of air trapping consequent to airflow obstruction. Parenchymal diseases produce a *'restrictive'* ventilatory defect, reducing TLC and VC, with RV being less affected (Table 11.7).

Test of respiratory muscle function

The ability of respiratory muscles to inflate and deflate the lungs is critically important. Respiratory muscle weakness (whether neurogenic, such as Guillain-Barre or diaphragmatic paralysis, or myogenic, such as myasthenia gravis or primary myopathies) can result in dyspnea and mimic a restrictive ventilatory pattern. Measurement of peak inspiratory (PI_{max}) and peak expiratory maximal mouth pressures (PE_{max}) by sucking at and breathing out respectively against the shutter of a pressure transducer device is the best simple test of respiratory muscle strength.

Carbon monoxide gas transfer tests (diffusing capacity)

To measure carbon monoxide diffusion capacity (DL_{CO}) the subject inhales a gas mixture of helium and 0.03 per cent carbon monoxide from RV to TLC and holds breath for 10 seconds and then slowly exhales. The change in concentration of gases as measured by an automated equipment predicts DL_{CO}. Diffusing capacity is reduced in interstitial disease (when alveolar capillaries are reduced), in air space disease associated with ventilation perfusion mismatch

(such as pneumonia), in heavy smokers and in the presence of significant anemia.

Exercise tests

Exercise testing is a good method of assessing integrated cardiorespiratory system function. A simple test is a 6 or 12 minute walking test where oxygen saturation is determined with a portable pulse oximeter before and after a walk. Desaturation on exercise indicates a ventilation perfusion mismatch; it is seen in both interstitial and obstructive lung diseases. A more complicated test involves ploting heart rates and minute ventilation against oxygen uptake with estimation of the respiratory quotient (VCO_2/VO_2) during graded exercise performed on a treadmill or a cycle ergometer.

A normal response includes a linear increase in heart rate and an increase in minute ventilation, initially by an increase in tidal volume (till it reaches 60% of VC) and then solely by an increased respiratory rate.

A disproportionately elevated minute ventilation at rest or at low workload is abnormal and indicates an increase in ventilation perfusion mismatch and increased dead space.

Arterial blood gases

A sample of arterial blood is obtained from the brachial or radial artery in a heparinised syringe with a fine needle (with adequate local anaesthesia). The syringe should be placed in ice immediately and the sample analysed for arterial pH and the tensions of arterial oxygen (P_aO_2) and carbon dioxide (P_aCO_2). The alveolar oxygen tension (P_AO_2) can be estimated if the partial pressure of inhaled oxygen (PIO_2) and the respiratory exchange ratio are known (see Table 11.8). The alveolar arterial O_2 difference can then be calculated; this difference is a measure of gas exchange efficiency. In normal subjects this is usually less than 10 mmHg and may increase with age to about 20–30 mmHg in older subjects. When hypoxemia is due to hypoventilation, the P_AO_2 : P_aO_2 ratio remains normal. This is so because the fall in PO_2 is due to a rise in PCO_2 and the calculated P_AO_2 should fall to the same extent as the P_aO_2. When hypoxemia is accompanied by a widened alveolar-arterial difference, ventilatory exchange is suboptimal. The precise pathophysiologic mechanism can be elucidated by repeating blood gases with the patient on supplemental 100 per cent oxygen. A narrowing or normalisation of the alveolar-arterial oxygen difference indicates that an abnormal diffusion or a ventilation perfusion inequality is a pathophysiologic mechanism.

Non-invasive oximetry Oximeters are light weight sensors that clip on to the ear or fingertip and measure oxygen saturation (SaO_2). Since the absorption spectra of oxyhemoglobin and deoxyhemoglobin differ, oximeters can compute the oxygen saturation by measuring the ratio of the two. Commercial oximeters are fairly accurate (± 4%) for saturation levels above 80 per cent. Oximetry is not a sensitive guide to gas exchange in patients with high baseline P_aO_2 values due to the sigmoid shape of the O_2 dissociation curve, whereby large changes in P_aO_2 may result in little change in SaO_2.

Bronchoscopy

Fibreoptic bronchoscopy combines the advantages of flexibility, and resultant maneuverability, and high quality optics in an instrument which is made of light-transmitting glass fibres and returns a magnified image through a system of lenses to the observer's eyes. The flexible bronchoscope is about 60 cm long with its distal 2.5 cm capable of swinging through an arc of upto 250 degrees (Fig 11.12). This instrument permits visualisation of segmental and subsegmental bronchi.

The procedure is simple and safe when performed by a trained operator. After *premedication* with atropine (0.6–1 mg atropine i.m.) and topical upper airway anesthesia with 4 per cent lignocaine, the instrument is passed transnasally through one nostril, supplementary

Table 11.8 Clinical interpretation of arterial blood gases in respiratory medicine

Step 1	Estimate PIO_2
PIO_2	= (Barometric pressure – Water vapour pressure) x 0.21*
where *	= percentage of O_2 under normal conditions at sea level,
PIO_2	= (760 – 47) × 0.21
	= 149.7 mmHg
Step 2	Estimate P_AO_2
P_AO_2	= $PIO_2 - (P_ACO_2/R)$
where R	= Respiratory exchange ratio. Using R = 0.8, P_ACO_2 = 40, at sea level,
P_AO_2	= 149.7 – (40/0.8)
	= 99.7 mmHg
Step 3	Estimate $P_AO_2 - P_aO_2$ (alveolar-arterial oxygen difference); normally it is less than 10 mmHg
	• if P_aO_2 is low (hypoxemia) and the difference < 10 mmHg
	hypoventilation is likely: check PCO_2; it is usually high
Step 4	† if P_aO_2 is low and the difference wide, repeat ABG with inhalation of 100% oxygen

† if (A-a) difference is still wide, intrapulmonary shunt exists; if (A-a) normalises, V/Q mismatch or abnormal diffusion is the likely pathogenetic mechanism

oxygen being administered by a nasal catheter through the other nostril. *Brushes* or *catheters* can be passed through the instrument to obtain specimens of bacteriologic culture and cytologic examinations. Specially designed *forceps* can also be negotiated through the instrument for transbronchial pulmonary biopsies; other forceps and *baskets* can be similarly inserted for retrieving foreign bodies.

The bronchoscope is used for diagnostic as well as therapeutic purposes. Its *diagnostic* uses include investigation of hemoptysis especially in a smoker over the age of thirtyfive, obtaining biopsy specimens of central tumours, investigating unresolved pneumonitis or lung abscesses to obtain cultures and to rule out a mechanical obstruction such as due to a malignancy, preoperatively in most patients with lung cancer for staging the disease, for obtaining a lavage of the alveoli (known as broncho-alveolar lavage) in patients with interstitial lung disease for assessing disease activity, and in others who are immunosuppressed for the diagnosis of infections such as those due to Pneumocystis. The bronchoscope has a *therapeutic* role in retrieving foreign objects, removing inspissated mucous plugs (thereby relieving atelectasis) and for plugging bronchopleural fistulae. The fibreoptic bronchoscope is also used in *photodynamic* laser therapy of small mucosal tumours. The violet light of the bronchoscope detects tumours that take up hematoporphyrin derivatives (injected intravenously) and these are 'laser ablated'. Recently, the fibreoptic bronchoscope has also been used as an effective alternative to bronchial artery embolisation in the treatment of persistent hemoptysis. The bleeding site is located and topical thrombin or fibrinogen instilled to control the bleeding. Radioactive iridium implants can be inserted into intrabronchial tumours with the fibreoptic bronchoscope especially to treat troublesome local recurrences (*brachytherapy*). The rigid bronchoscope has been used for treating massive hemoptysis.

Pleural Biopsy

Pleural biopsy is performed percutaneously under local anesthesia with an Abrams Cope

needle. The parietal pleura is biopsied in such cases and the procedure is a safe one in the presence of significant amounts of pleural fluid. The biopsy may reveal histopathologic features of tuberculous pleuritis (in 60 per cent of patients with tuberculous pleural effusion) or of malignant pleural invasion (in 40–80 per cent of patients with a lung malignancy and pleural effusion). Culture of biopsy tissue for *M. tuberculosis*, in a tuberculous effusion enhances the diagnostic yield to 80–90 per cent. Primary pleural tumours, however, may be missed due to a focal nature of the disease.

An alternative procedure to blind pleural biopsy is a thoracoscopy-guided biopsy. A fibreoptic bronchoscope is inserted through an intercostal incision under local anesthesia and the pleural surface inspected and a biopsy of diseased segments taken. Pleural biopsy carries a small but definite risk of pneumothorax and pulmonary hemorrhage.

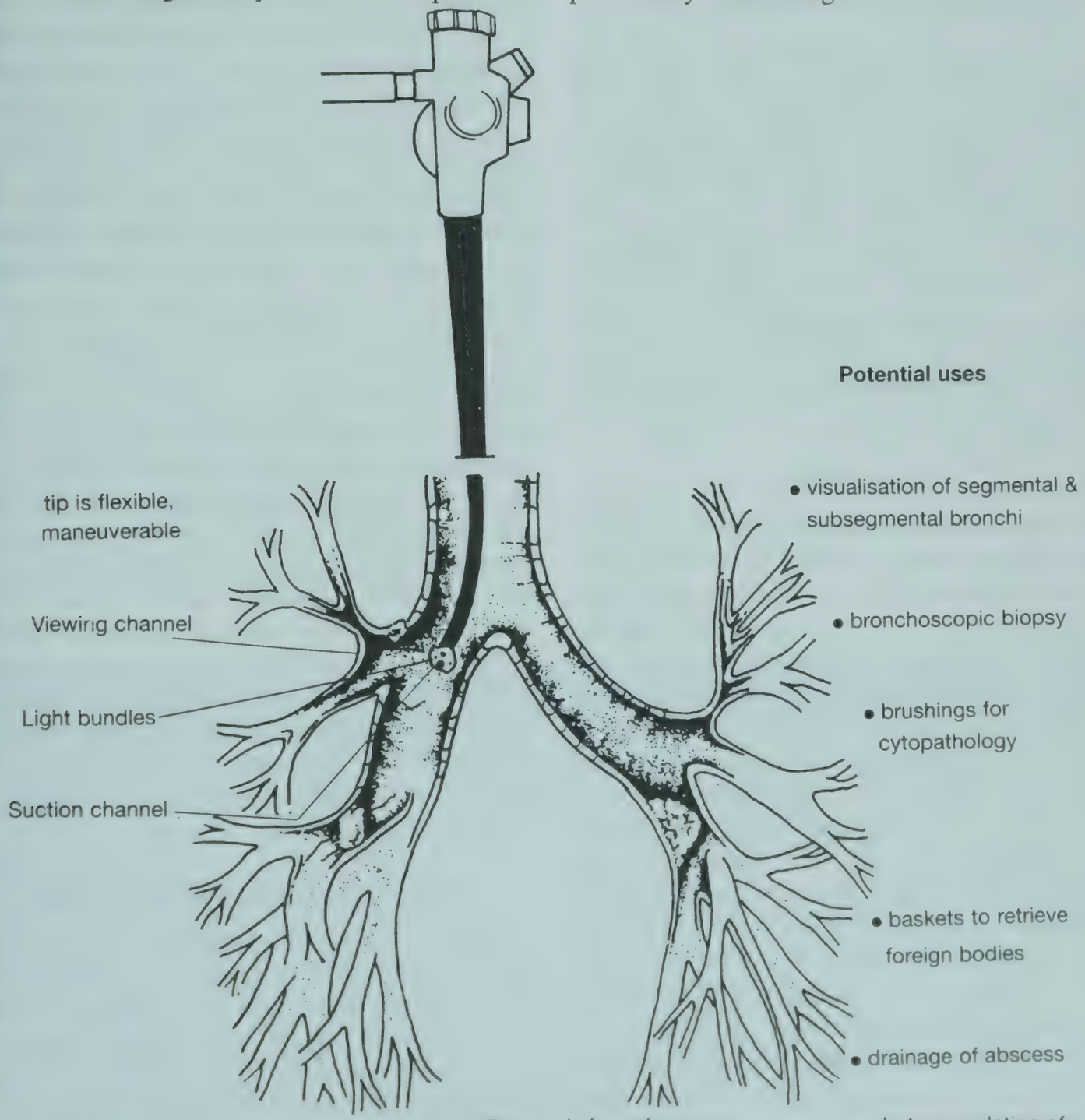


Fig 11.12 Fibreoptic bronchoscopy

Mediastinoscopy

In this procedure a tube is passed into the mediastinum through an incision in the sternal notch in order to sample anterior mediastinal lymph nodes. This has proved more useful than scalene node biopsy for the diagnosis of tuberculosis, sarcoidosis, and lymphoma. This procedure also helps in assessing the spread of bronchogenic carcinoma.

Percutaneous Fine Needle Aspiration

Peripherally located pulmonary lesions are relatively inaccessible to the fibreoptic bronchoscope. An alternative technique is fluoroscopy-guided fine needle aspiration. A thin, small-bore 23–25 gauge needle (like the Zavala skinny needle) can be used for this purpose. The procedure has a higher diagnostic yield for malignant lesions (about 80–90 per cent) as compared to inflammatory lesions like pneumonia. There is, however, a 20–30 per cent incidence of pneumothorax and a 20 per cent incidence of hemoptysis.

Lung Biopsy

Lung tissue can be obtained for histopathologic studies using cutting needles or trephine drill biopsies percutaneously, by brush biopsies with a bronchoscope, or by an open limited thoracotomy. Percutaneous biopsies are not attempted nowadays because of the high risk of pneumothorax and pulmonary hemorrhage. A recent study using a Mausser core needle biopsy has however reported a high diagnostic yield (90%) with a low complication rate (15%). This has rekindled interest in the procedure. Lung biopsy is useful for histologic assessment of pulmonary vascular disease in pulmonary hypertension, evaluation of interstitial lung disease, mass lesions and inflammatory lesions. Coordination between the surgeon, the pathologist and the microbiologist is required for proper and prompt processing of the tissue obtained.

Computerised Tomography (CT)

Computerised tomography provides excellent anatomic details of the hilum, hilar structures, pulmonary parenchyma and the pleura.

Conventional CT results in thick slices (typically 10 mm) with a loss of spatial resolution (blurred images). High resolution computerised tomography generates thinner slices (typically 1.5 mm) but results in more noise (grainier images). Chest CT scan helps define abnormalities seen on plain X-ray films and also screens for occult disease in patients with a high probability of the same. Thus, intrathoracic tumours (such as bronchogenic carcinoma, or lymphoma) can be staged and occult tumours detected (like thymomas in patients with myasthenia gravis). CT densitometry now permits a differentiation between malignant lymph nodes and hyperplastic lymph nodes. Radiotherapy can also be better planned and resectability of a lesion better judged with the help of the CT. The CT scan performed with a bolus of intravenous contrast, known as a contrast CT, helps differentiate hilar lymph node enlargement from hilar vascular structures. The airways are also delineated well with the chest CT. Anatomical dilatation of bronchi (as in bronchiectasis) can be well-defined. The CT scan is also helpful in detecting occult parenchymal involvement (of nodules as small as 3 mm) in interstitial lung disease. Pleural pathology such as asbestos related plaques or neoplasia can be similarly well-delineated. Defects of the diaphragm and peridiaphragmatic masses, or fluid collections can be identified with the help of the thoracic CT scan.

Magnetic Resonance Imaging (MRI)

MRI is as yet an investigational tool in pulmonary disease. It is more sensitive than CT in detecting hilar and mediastinal lymphadenopathy. Its role in pulmonary parenchymal disease is still being evaluated. It has a theoretical advantage over CT scan in that no ionising radiation is used.

Radionuclide Pulmonary Imaging

Perfusion scanning is performed with 99 technetium labelled serum albumin microspheres (or microaggregates) injected intravenously with the patients being scanned in several positions with a gamma camera. Ventilation scans are performed with Xenon^{133} ($t^1/_2$ = 5.7d), krypton ^{81m} ($t^1/_2$ = 13 seconds) or technetium 99 DTPA aerosols. Xenon^{133} is the most commonly used. The main indication for ventilation-perfusion scanning is in the diagnosis of pulmonary embolism, wherein the presence of multiple segmental perfusion defects with a normal ventilation scan is diagnostic of pulmonary embolism.

Gallium^{67} scan has been used to identify areas of infection or neoplasia in the chest and to assess the activity of infiltrative lung disease like sarcoidosis.

Lung Lavage

Lung lavage includes *bronchial lavage* (which is performed to remove sticky secretions and mucous plugs from the larger bronchi) and *bronchoalveolar lavage* (BAL).

BAL is performed by wedging a fibreoptic bronchoscope into a third or fourth order bronchus and infusing about five 20 ml aliquots of sterile isotonic saline and sucking back the effluent (usually 40–60 ml/100 ml infused). The normal and abnormal cellular contents (in disease) are shown in Table 11.9. Interpretation of the results of bronchoalveolar lavage requires adjustment for the age, sex and smoking status of the individual, all of which can produce qualitative and quantitative changes in the lavage cell count. Standardisation of the lavage technique and laboratory processing of the specimen are essential for reliable results. BAL helps in the diagnosis of interstitial lung disease, in predicting response to therapy, and in prognostication of diffuse lung disease. It can also help in establishing the cause of pulmonary infiltrates in the immunocompromised (as in the acquired immunodeficiency syndrome). BAL has also shed light on latent pulmonary involvement in primary biliary cirrhosis; an intense lymphocytic alveolitis akin to sarcoidosis has been observed.

It must be remembered however that BAL does not constitute a liquid lung biopsy, that is, not all the inflammatory cells present in the lung are sampled by bronchoalveolar lavage. Thus, BAL does not sample the epitheloid cells so prominent in sarcoid granulomas or the giant cells present in the alveoli of hardmetal worker's lung disease.

Table 11.9 Cellular constituents in BAL fluid

Category	*Number of cells (x 10^8 / ml)*	*Lymphocytes (%)*	*Macrophages (%)*	*Neutrophils (%)*	*Eosinophils (%)*	*Mast cells (%)*
Normal	14	8*	90	<1	<1	<1
Smoker	→	→	→	↑(2–4)	–	–
Idiopathic pulmonary fibrosis	↑↑	→	↓	↑↑	–	–
Extrinsic allergic alveolitis	↑↑	↑	↓	↑	↑	–
Sarcoidosis	↑↑	↑↑	↓↓	→	–	–

* normally 70% T lymphocytes, 5–10% B lymphocytes, 7% natural killer cells, 5% untypable, with a $T_{helper/suppressor}$ ratio = 1.5–1.8; ↑ = increased, ↓ = decreased, → = unchanged

KEY CONCEPTS

Sputum examination

- Examination of the sputum is helpful in the diagnosis of bacterial pneumonia (Gram staining), pulmonary tuberculosis (Ziehl-Nielsen stain) and lung cancer (cytologic examination).
- A sputum sample is a reliable sample of lower respiratory tract secretion if there are >25 neutrophils but <10 squamous cells/low power field.

Chest X-ray

- A PA chest film is superior to an AP film (avoids geometric magnification), and a film obtained with the patient erect is superior to one with the patient supine (better assessment of vasculature and parenchyma).
- A *consolidation* is a pulmonary opacity due to the filling of air spaces with fluid or an inflammatory exudate. The presence of an *air bronchogram* is diagnostic.
- An area of pulmonary *collapse* also appears as an opacity but there is associated evidence of a loss of volume (mediastinal shift, crowding of ribs).
- The earliest sign of a *pleural effusion* on a PA chest film is blunting of the cardiophrenic angles (usually indicates >300 ml fluid). A *subpulmonic* effusion appears as a raised hemidiaphragm.
- *Unilateral hilar lymphadenopathy* is seen in pulmonary tuberculosis, fungal infections, tularemia, psittacosis or a lymphoma. *Bihilar lymphadenopathy* is suggestive of sarcoidosis or a lymphoma.

Pulmonary function tests

- PFT include spirometry, tests of dynamic lung function, ABG and exercise testing.
- *Obstructive lung disease* is characterised by reduced FEV_1, VC, FEV_1/VC (<0.70), and increased TLC. On the other hand, *restrictive lung disease* is characterised by reduced VC, TLC, DL_{CO}, and normal FEV_1/FVC (>0.70). FEV_{25-75} is less effort-dependent, reflects the status of small airways and therefore, is a more sensitive sign of early airway disease.
- Simple *spirometry* is usually sufficient for distinguishing restrictive from obstructive lung disease. A low vital capacity in the presence of normal flow rates suggests restrictive lung disease. DL_{CO} is a measure of the adequacy of gas exchange across the alveolocapillary membrane. Periodic assessment of VC and DL_{CO} is used for monitoring the clinical progression and the response to the treatment of interstitial lung disease.
- *Dynamic flow volume curves* are also useful for distinguishing *intrathoracic* obstruction from *extrathoracic* obstruction of airways.
- *Arterial blood gas analysis:* P_aCO_2 indicates the ventilatory status of a patient. Hypercapnia suggests hypoventilation whereas hypocapnia indicates hyperventilation. The *alveolar-arterial O_2 difference* (normal is <10 mmHg) is a measure of the degree of V/Q mismatch.
- Weakness of the respiratory muscles can be evaluated with the MVV (maximal voluntary ventilation) parameter, and by measuring the peak inspiratory pressures and the FVC.

Bronchoscopy

- In this technique a flexible fibreoptic bronchoscope is inserted into the airways through the mouth to visualise the larynx, upper airways and the segmental and subsegmental bronchi. Bronchial washing, brushings, lavage, and biopsy may be obtained using this method.
- The technique may be used for diagnostic and therapeutic purposes. Diagnostic uses include investigating suspected pulmonary cancer, staging of bronchogenic carcinoma, evaluating the source of pulmonary bleeding in a patient with hemoptysis, investigating pulmonary infiltrates (especially in HIV-positive individuals), and diagnosing the etiology and monitoring the course of interstitial lung disease.
- Therapeutic purposes include removal of a foreign body, drainage of inspissated secretions, and laser photocoagulation of bleeding mucosal areas.

Thoracic CT scan

- The CT scan is the diagnostic procedure of choice for evaluating mediastinal tumours, staging lung cancer, investigating pleural disease and assessing hilar, paratracheal and subcarinal lymphadenopathy.
- The CT scan can help distinguish vascular from non-vascular structures at the hilum.
- A high-resolution CT scan helps to confirm the presence, extent, and activity of interstitial, alveolar and airway disease.
- CT densitometry may have a role in determining the presence or absence of calcium in solitary pulmonary nodules.

Thoracic MRI scan

- An MRI is equivalent to a CT scan in evaluating lung cancer.
- Like CT, it is useful in investigating mediastinal tumours and can distinguish between vascular and non-vascular structures at the hilum.
- It is more expensive than CT and its role in pulmonary disease remains investigational.

Bronchoalveolar lavage

- In this technique, a fibreoptic bronchoscope is used to lavage the alveoli with saline. The returning fluid contains cells presumably of alveolar origin. The nature of the cells and the relative proportion of different cell populations provide clues regarding the nature of the parenchymal disease and may predict the response to steroid therapy.

11.4 Obstructive airway disease and respiratory failure

Chronic Obstructive Airway Disease

Chronic obstructive airway disease (COAD) has been defined as a group of diseases characterised by persistent slowing of airflow during expiration. The term includes both chronic bronchitis and emphysema.

Chronic bronchitis is defined as a clinical disorder characterised by excessive mucous secretion in the bronchial tree manifested by chronic recurrent productive cough for more than three months in a year for two consecutive years. This definition is based on the history of the patient. *Emphysema* is defined as an anatomic alteration of the lung, characterised by abnormal enlargement of the airspaces distal to the terminal, non-respiratory bronchioles and accompanied by destructive changes in the alveolar walls. This definition is based on histopathological changes.

Epidemiology Studies in the USA and Europe indicate that about 10 per cent of individuals in the general population have significant airflow obstruction. There is a male predominance due to greater number of males being smokers (smoking being a key factor in the pathogenesis of the disorder). Calculations suggest a significant social and economic impact of disability due to COAD. In India 'beedis', cigarettes and 'hukka' are all responsible for COAD in the rural areas. The practice of lighting 'choolas' in poorly ventilated homes accounts for a high prevalence of the disorder in non-smoking rural women. A high prevalence of both urban and industrial air pollution contributes to the pathogenesis of the disorder in the cities.

Pathogenesis It is currently believed that the pathogenesis of chronic bronchitis and of emphysema are quite different. Chronic bronchitis is associated with bronchiolar inflammation appearing in individuals with an 'asthmatic bronchitic' predisposition. These individuals have elevated serum IgE levels but unlike in patients with asthma, the levels are lower, there is no seasonal variation and the IgE is not specific for aeroantigens. There is a heightened bronchial responsiveness possibly related to bronchial inflammation (with polymorphonuclear cells and mononuclear cells, not eosinophils). Smoking plays an important role, presumably by way of a tobacco-induced increased airway permeability to antigenic material since antigens thus gain access to immunoreactive cells.

Emphysema on the other hand is related to alveolar inflammation, is almost always associated with cigarette smoking and is unrelated to asthmatic characteristics such as an elevated serum IgE or eosinophil count. Smoking causes alveolar inflammation by depressing alveolar macrophage function, retarding mucociliary clearance, reducing the functional integrity of the pulmonary surfactant and disturbing the protease-antiprotease balance of the alveolar wall. Individuals with a homozygous *deficiency* of α_1-antitrypsin develop

emphysema early in life due to autodigestion of the pulmonary tissue by the unopposed action of naturally occurring proteases.

Smoking in pack years (number of packs smoked per day multiplied by number of years a patient has smoked) is quantitatively related to pathologic changes in the lung.

Pathology and pathophysiology In chronic bronchitis, the small airways are the most affected and demonstrate mucous plugging, mucosal inflammation, peribronchiolar fibrosis and varying degrees of mucous gland hyperplasia. In emphysema the changes are classified as either centrilobular or panlobular. *Centrilobular*, also called *centriacinar emphysema,* starts at the centre of the lobule with destruction of the respiratory bronchiole resulting in a loss of tissue support for the airways. The airway consequently tends to narrow and collapse dynamically during expiration. It is often associated with smoking and changes of chronic bronchitis. *Panlobular emphysema* evolves from dilated alveolar ducts at the periphery of the lobules leading to markedly enlarged airspaces.

The pathophysiologic hallmark of COAD is hypoxemia due to a ventilation-perfusion mismatch (due to airway obstruction) and diminished diffusion capacity due to destruction of alveolocapillary membrane. Patients increase their minute ventilation to prevent hypercapnia till a point is reached when a further increase in ventilation becomes impractical either due to muscle fatigue or because of a high energy expenditure. Hypercapnia then results and combined with hypoxemia and acidosis, causes pulmonary vasoconstriction and consequent pulmonary arterial hypertension. Patients with emphysema have proportional losses of ventilation and perfusion so that a mismatch and consequent hypoxemia is less common in them as compared to patients with chronic bronchitis.

Clinical features Two classic presentations of COAD are known. Patients with Type A COAD have predominant emphysema and are known as the *pink puffers.* The clinical history is one marked by a progressive exertional dyspnea with scant or absent cough and expectoration. The physical examination reveals a barrel shaped chest with diminished breath sounds. Patients with Type B COAD have predominant chronic bronchitis and are called the *blue bloaters.* The clinical history is one of chronic cough and expectoration. Physical examination may reveal the presence of cyanosis with prominent wheezing or rhonchi on auscultation of lung fields. Nicotine stains on the fingers may suggest a chronic smoking habit.

Investigations The chest X-ray may show hyperinflation, flat diaphragms with a small cardiac silhouette and a loss of vascular markings in a patient with predominant emphysema. Patients with chronic bronchitis may show radiologic evidence of thickened bronchial walls. Pulmonary function tests in Type A COAD patients reveal mild hypoxia, hypocapnia and a decreased diffusion capacity with only a mild increase in airway resistance. In Type B COAD patients, there is often severe hypoxemia, hypercapnia and a preserved diffusion capacity but a markedly elevated airway resistance. The FEV_1 is of prognostic importance. The normal yearly loss of FEV_1 in COAD patients is 50–75 ml (roughly twice the normal rate of decline). Patients with an initial FEV_1 less than 0.75 L have a five-year survival of 25 per cent whereas those with an initial FEV_1 of 1 L have a 50 per cent five-year survival.

Long-term management The aims of long-term management are to provide symptomatic relief from hypoxemia and its complications, to take steps to decrease the frequency of acute exacerbations and to slow the rate of progression of the disease.

1. Smoking is to be strictly prohibited, and this requires patient education regarding the deleterious effects of tobacco. Nicotine gums

may be substituted and clonidine may be tried to help counteract nicotine withdrawal states.
2. The optimal bronchodilator treatment involves the use of inhaled beta 2 (β_2) agonists, inhaled ipratropium bromide (an anticholinergic bronchodilator) or oral theophyline alone or in combination.
3. There is some evidence to suggest that in subjects with disabling airway obstruction, a 2–3 week trial of corticosteroids may yield symptomatic benefit.
4. Domiciliary oxygen therapy in the form of continuous administration of oxygen is indicated when the resting arterial oxygen tension is consistently below 55 mmHg or the oxyhemoglobin saturation is less than 88 per cent.
5. When available, influenza and pneumococcal vaccine can be administered to patients to reduce the risk of intercurrent pneumonitis.
6. Exercise training can help improve the patient's exercise capacity, though lung functions may not improve.

Management of acute exacerbation The measures instituted are similar to those for an episode of acute bronchial asthma (discussed later) with the important difference being that supplemental oxygen is used with caution to maintain a P_aO_2 of 55–60 mmHg. A low flow oxygen delivery system (1–3 litres/min by nasal cannula) is adequate. In these subjects hypoxia is an important ventilatory stimulus and high concentrations of oxygen may remove this stimulus and precipitate a state of hypoventilation, hypercapnia and altered sensorium (CO_2 narcosis).

Bronchial Asthma

Bronchial asthma is a disorder characterised by *airway hyperresponsiveness* to a number of ubiquitous inflammatory triggering factors. Bronchospastic triggers such as, exercise, cold air, hyperventilation, pharmacologic and psychogenic stimuli produce airway narrowing in proportion to the level of airway hyperresponsiveness, but do not enhance airway responsiveness. Inflammatory triggers such as, allergens or viral infections induce asthma by enhancing airway responsiveness.

Bronchial hyperresponsiveness is defined as an increased bronchoconstrictor response to inhalational challenge with histamine or methacholine. It is observed in 5 per cent of normal individuals, in 15 per cent of non-atopic individuals with a family history of asthma and in 100 per cent of those with clinical asthma.

Pathogenesis Bronchial smooth muscle tone and bronchial secretions are under the control of humoral and neural mechanisms. Normal bronchial tone increases in the early morning ('morning dipping' of the peak expiratory flow rate), the time when most acute exacerbations and most fatalities due to asthma occur. Cholinergic influences are mediated through vagal impulses and the acetylcholine released acts on muscarinic receptors (subtypes M1 and M3 in the peripheral lung, M2 in the central airway)[1] resulting in increased intracellular cyclic GMP. This results in bronchoconstriction and bronchial secretion. Antagonists inhibit the release of acetylcholine at the neuronal terminal. The circulating catecholamines act on β_2 adrenergic receptors, increase intracellular cyclic AMP levels and are bronchodilators and antisecretory. The calcium flux across cell membranes is important in the final effector pathway of smooth muscle contraction and mast cell degranulation. There are also other nerves, the non-adrenergic, non-cholinergic *(NANC)* nerves (C fibre afferent nerve endings) that release inflammatory neuropeptides into the bronchial wall. The neuropeptides include neurokinin A and calcitonin G-related peptide (bronchoconstrictors), vasoactive intestinal polypeptide (a bronchodilator) and substance P (which increases microvascular permeability and

[1] M1 receptors are found on parasympathetic ganglia, M2 receptors on cholinergic nerves and M3 receptors on airway smooth muscle and mucous glands.

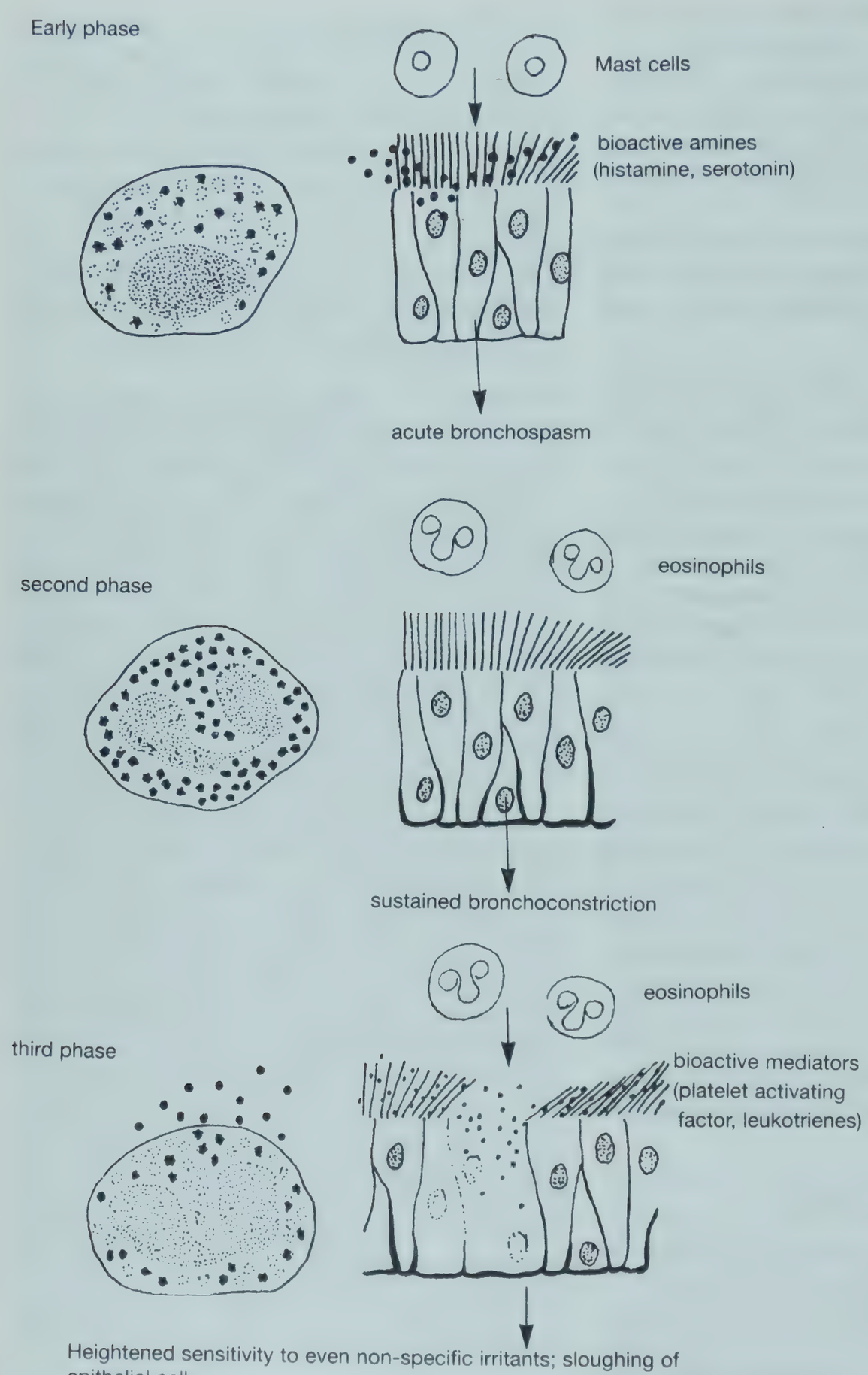


Fig 11.13 Pathophysiology of asthma

muocus secretion). A deficient release of VIP has been observed during acute asthmatic attacks.

Allergenic stimuli produce a biphasic clinical response in asthmatics: an *early asthmatic response* (EAR) and a *late asthmatic response* (LAR) (Fig 11.13). The EAR develops within minutes of antigenic exposure, peaks at 10–30 minutes and lasts for about 1.5–3 hours. It is a classic antigen-antibody reaction wherein the mast cells presensitised to the allergen are triggered by the 'antigen-specific IgE antibody' (reagin)-antigen complex on their surface. The mast cells release histamine, heparin, trypsin, prostaglandin D_2 and leukotriene C_4; additional mediators released include the eosinophil and neutrophil chemotactic factors and platelet activating factors (PAF). The late asthmatic response begins 3–4 hours after antigenic challenge, peaks at 8–12 hours and lasts for 1–2 days. This phase is associated with the development of airway inflammation. Initial cellular infiltrates consist of macrophages, followed subsequently by eosinophils and lymphocytes. Macrophages release PAF and leukotriene B_4 (a chemoattractant for eosinophils). The lymphocytes release lymphokines, of which interleukin 3 and 5 attract mast cells and eosinophils, respectively. The leukotrienes released include leukotrienes C_4, D_4 and E_4; the combination was formerly called the slow reacting substance of anaphylaxis (SRS-A).

The three components of the asthmatic response, therefore, include 1) a *cellular* component involving eosinophils, neutrophils monocytes, mast cells and platelets; 2) a *vascular* component characterised by hyperemia, stasis interstitial edema and an increased microvascular permeability; and 3) a *morphological* component characterised by hypertrophy of mucous glands and muscle, thickening of basement membrane, shedding of cells and inspissation of secretions. Recent autopsy studies have demonstrated the presence of subepithelial fibrosis in the bronchi of patients with asthma.

Epidemiology Bronchial asthma affects about 5 per cent of the general population. Roughly half the cases have an onset in the first decade of life, with males being affected twice as often as females. A classification into an *extrinsic* form which is seasonal, IgE mediated, occurs in young atopic individuals with a positive skin prick test to allergens, and an *intrinsic* form which is perennial, and occurs in older non-atopic individuals, has been suggested. Recent evidence has challenged this concept with the demonstration that if an age-related IgE decrement is taken into account, even individuals with so-called intrinsic asthma have IgE levels well above that in the general population and, therefore, an allergic base.

Atmospheric pollutants can precipitate bronchial asthma (the so-called *Tokyo-Oklahoma asthma*) as can drugs like aspirin. Aspirin-induced asthma is associated with nasal polyposis and sinusitis. It is probably due to an excess production of leukotrienes, as aspirin-induced cycloxygenase inhibition results in increased channelling of arachidonic acid precursors into the lipooxygenase path. *Exercise-induced asthma* is presumably related to exertion-induced changes in air temperature and humidity which trigger bronchospasm. *Occupational asthma* is related to exposure to chemical agents (such as epoxy resins in plastic factories or toluene diisocyanate in varnishes and paints) that either induce bronchoconstriction directly or via degranulation of mast cells. It is characterised by a cyclic history, with symptoms becoming prominent towards the end of a work shift and an increase of symptoms after leaving the work site.

Nocturnal asthma refers to attacks that predominantly occur during the night. It has been related to recumbency, a diminished mucociliary clearance, nocturnal airway cooling, exposure to night-time allergens, gastroeso-

phageal reflux and a 'morning dip' in circulating epinephrine and cortisol.

Pathophysiology Increased airway resistance is the pathophysiologic hallmark of an asthmatic attack. In addition, the patient must breathe at high lung volumes to keep his airways open, resulting in an increased load of breathing. The highly negative pleural pressures, that must be generated to inflate the lung, can result in an increased afterload on the left ventricle. Thus *pulsus paradoxus* may be present in severe attacks of asthma. The hypoxemia resulting from bronchospasm can lead to pulmonary hypertension during an acute episode of asthma, manifested on the surface electrocardiogram as right axis deviation and peaked P waves.

Management of acute severe asthma (see also Chapter 11.9) The aims of treating an acute severe attack of asthma are to prevent death, to restore the patient's condition to a level of optimal pulmonary function and to prevent further relapses. While examining the patient in the emergency room, life-threatening features are identified (Table 11.10); if present, both arterial blood gases and expiratory flow rate measurements are obtained. A chest roentgenogram may be obtained subsequently to look for infection, edema or pneumothorax.

1. Oxygen is administered with a nasal cannula using the highest concentration available, as CO_2 retention is not a danger.
2. β_2 agonists are administered by inhalation using nebulisers, if available (Fig 11.14), or with metered dose inhalers. The dosage and agents available are shown in Table 11.11.
3. If the patient is unable to use aerosolised drugs, subcutaneous epinephrine (0.3 ml of 1:1000 dilution) or terbutaline (0.25 mg) may be administered.

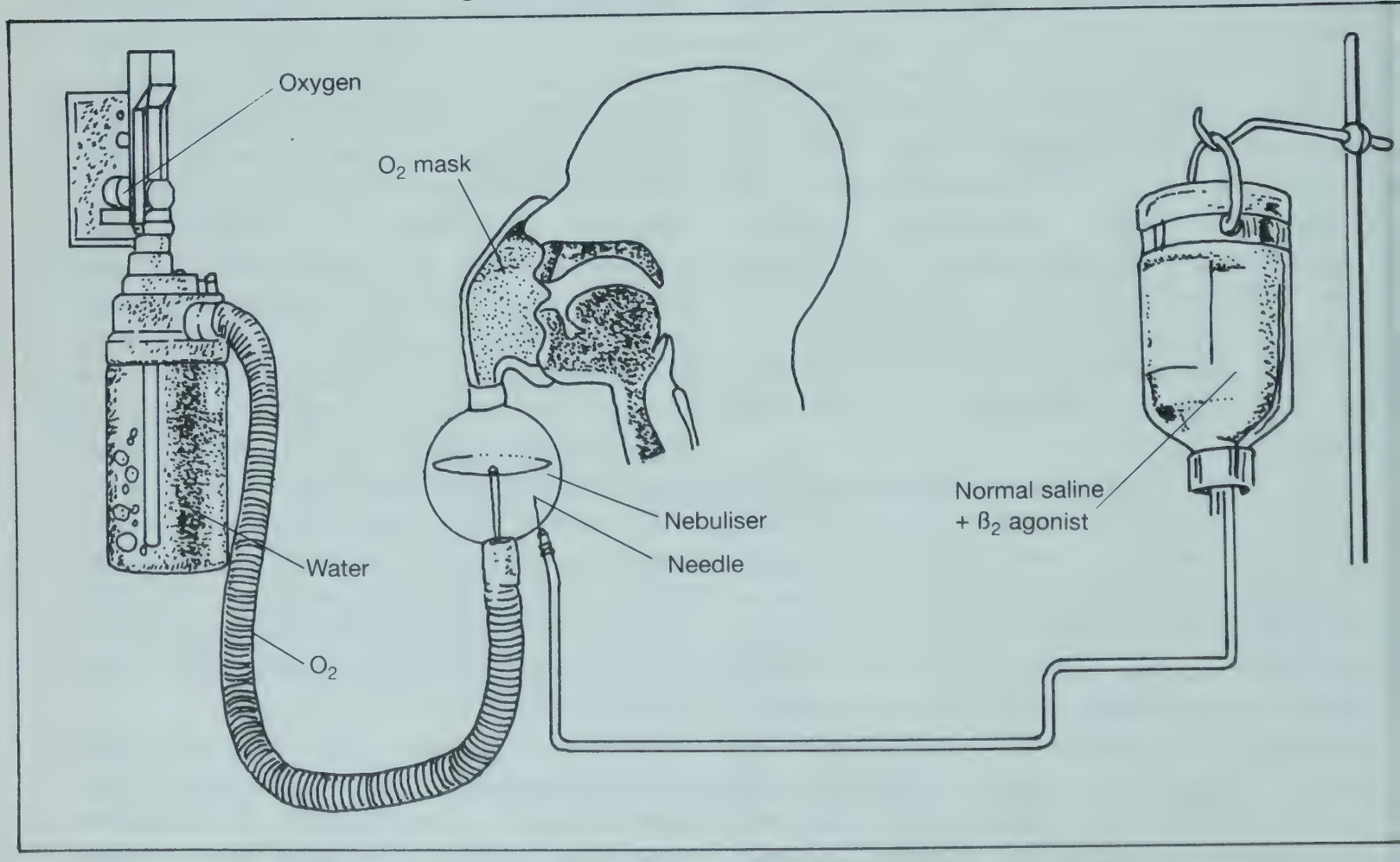


Fig 11.14 Administration of beta-adrenergic agonist by continuous nebulisation

Table 11.10 Recognising life-threatening asthma
British Thoracic Society Guidelines

'Potentially' life-threatening asthma

- Inability to complete sentence in one breath
- Respiratory rate ≥25/min
- Tachycardia ≥110/min
- Inspiratory fall of systolic pressure >10 mmHg (pulsus paradoxus)
- PEFR <50% predicted, or <200 l/min

'Imminently' life-threatening asthma

- Silent chest on auscultation
- PEFR <33% predicted
- Cyanosis
- Bradycardia or hypotension
- Altered conciousness
- Normal [5–6 kPa, 36–45 mmHg] or high P_aCO_2
- Severe hypoxia ($P_a\,0_2$ <8 kPa [60 mmHg])
- Systemic acidosis

→ May require ventilatory assistance

4. Intravenous hydrocortisone (4 mg/kg) or methylprednisolone (1–2 mg/kg) or oral prednisolone (30–60 mg) should be administered immediately.
5. The use of intravenous aminophyline is controversial given the lack of data demonstrating its benefit and the potential risks in a patient already on oral theophylline. When used, the dose recommended is 0.5–0.9 mg/kg/hr (higher doses being required in young adults and smokers, a lower dose being required in the elderly, in the presence of congestive heart failure, liver disease or the use of drugs like erythromycin, cimetidine or quinolone antibiotics).
6. Salbutamol or terbutaline can be given as an intravenous infusion (12.5 μg/min, the rate of infusion being adjusted according to the clinical response of PEFR and heart rate).
7. The therapy is monitored with arterial blood gases, pulse oximetry and peak expiratory flow rates.
8. Sedatives and percussive physiotherapy are contraindicated.
9. Antibiotics are indicated if there is evidence of infection.
10. The indications for ventilatory support are shown in Table 11.10.
11. If the patient improves and an expiratory flow of more than 40 per cent predicted is achieved, the patient can be discharged on a regimen of oral steroids (prednisolone 20–40 mg/day for 1–3 weeks), inhaled β_2 agonists, an inhaled steroid and an oral bronchodilator (if required).
12. If the patient seen in the emergency room does not have features suggesting a severe attack of asthma and the measured PEFR is more than 40 per cent predicted, he can be observed in the emergency room for a few hours and treated with inhaled β_2, agonists. If repeat measurement reveals improvement, he can be discharged. If there is evidence of deterioration, the patient is hospitalised. A lower threshold for admission is appropriate if there is a history of rapid or recent onset with nocturnal worsening.

Management of chronic aevere asthma The aims of management are to restore normal function of the airways with minimal short- and long- term side effects.

1. If agents such as allergens, chemicals or drugs are known to precipitate acute attacks, these should be avoided.
2. A β_2 agonist (Table 11.11) should be used as required, inhalation being the preferred route of administration.
3. A patient who has nocturnal symptoms or who uses bronchodilators frequently will benefit from regular inhaled antiinflammatory drugs. Options include corticosteroids, disodium

Table 11.11 Drugs for treatment of asthma

Drug	Dosage				Comments and side effects
	Aerosol	Nebulised solution	Oral	Parenteral	
Sympathomimetic amines					
Adrenaline	–	–	–	0.3 ml of 1:1000 solution sc	avoid in elderly or if coronary disease is present; tremors, palpitation, arrhythmia
Terbutaline	500 µg 4 hourly	5 mg	5 mg tds	500 µg sc or im q 4–6 hours	tremors, arrhythmia
Salbutamol	200 µg 4 hourly	10 mg (0.3 cc of 5% solution)	2–4 mg tds	500 µg sc	- as above -
Isoproterenol	–	0.5 cc, 1:200 solution q 2 hrs	–	–	- as above - (not β_2–specific)
Methylxanthines					
Aminophylline	–	–	–	*loading*: 5–6 mg/kg iv over 20 mins *maintenance*: 0.5–0.6 mg/kg/hr	nausea, vomiting, seizures, hypotension, arrhythmia
Theophylline	–	–	200 mg qid	–	- as above -
Anticholinergic					
Ipratropium bromide	36 µg 6 hourly	–	–	–	less effective than β_2 agonists
Sodium cromoglycate	20 µg 6 hourly	–	–	–	for prophylaxis only
Corticosteroids					
Beclomethasone	100 µg 6 hourly	–	–	–	
Hydrocortisone	–	–	–	100–200 mg iv 6 hourly	steroids take time to act
Prednisolone	–	–	–		
	–	–	30–60 mg/day tapered × 14 days	–	

cromoglycate and nedocromil sodium. Inhaled corticosteroids are started at a low dose of 100–400 μg twice daily; the dosage can be increased to 2 mg with the use of a large volume spacer device to reduce oropharyngeal candidiasis.

4. If inhaled steroids do not control symptoms adequately, either inhaled ipratropium bromide, oral β_2 agonists and xanthines can be used. Higher doses of inhaled bronchodilators can also be used.
5. Immunosuppressive therapy (methotrexate) is currently under investigation.
6. Other drugs which are being evaluated include α antagonists (thymoxamine, indoramine), H_1 receptor antagonists (terfenadine, azelastine, loratadine) and troleandromycin (for the corticosteroid-resistant subjects).
7. The emphasis of management must be on objective self-monitoring by the patient of her peak expiratory flow and enlisting greater participation of the patient in the managment of her own condition.

Acute Respiratory Failure

Respiratory failure is defined as the inability to maintain arterial oxygen tension above 55 mmHg while breathing room air, with or without the presence of carbon dioxide retention (P_aCO_2 greater than 50 mmHg). When the onset is sudden, respiratory failure is said to be 'acute'.

Pathophysiology Respiratory failure may be due to *oxygenation failure* or *ventilatory failure* (Table 11.12). In oxygenation failure, the transfer of oxygen from the alveolar gas to the pulmonary capillary blood is affected, the alveolar-arterial oxygen tension difference is increased and this may be due V/Q mismatch or due to intrapulmonary shunts. The P_aCO_2 may or may not be elevated. In ventilation failure, the P_aCO_2 is elevated, the pH is less than 7.35 and the alveolar-arterial oxygen tension difference may remain normal. It is usually due to failure of the chest bellows, secondary to neurologic disease.

Table 11.12 Causes of respiratory failure

Oxygenation failure	*Ventilatory failure*
A. Ventilation-perfusion mismatch	A. Decreased minute ventilation
a. Obstructive airway disease	a. CNS depression
	Drug overdose
	Cerebrovascular accident
	Hypothyroidism
b. Parenchymal disease	b. Neuromuscular disease
infections	Guillain-Barre syndrome
embolism	Myasthenia gravis
B. Intrapulmonary shunt	Tetanus
a. Non-cardiogenic pulmonary edema (ARDS)	c. Obesity-hypoventilation syndrome
1. Aspiration	B. Increased dead space ventilation
2. Inhalation injury	
3. Narcotic drugs (heroin, methadone)	
4. Non-narcotic drugs	
5. Immunologic injury (SLE, Wegener's granuloma)	
6. Infections	
7. Sepsis	
8. Postcardiopulmonary bypass	

ARDS : Adult respiratory distress syndrome

Both types of respiratory failure coexist in the setting of chronic obstructive airway disease where hypoxia caused by ventilation-perfusion mismatch, is accompanied by hypercapnia due to alveolar hypoventilation.

In the *adult respiratory distress syndrome,* the injury is often of a systemic nature (such as sepsis or pancreatitis) and pulmonary dysfunction is only a part of what is actually a *multiple organ failure syndrome;* cerebral dysfunction, renal dysfunction and circulatory abnormalities may coexist.

Clinical features The clinical picture is one of the underlying inciting disorder and includes features of hypoxemia, hypercapnia and respiratory distress. *Hypoxemia* results in impaired mentation and rapid breathing. Cyanosis appears with severe hypoxemia when the P_aO_2 falls below 60 mmHg and the oxygen saturation falls precipitously thereafter. *Hypercapnia* also causes clouded mentation, muscle twitching (*asterixis* and 'flap'), increased cerebrospinal fluid pressure (resulting in papilledema) and cerebral vasodilation manifesting as headache. An excess of carbon dioxide accumulation can result in a stuporose state known as *CO_2 narcosis.*

Management The basic aims of management of acute respiratory failure are to relieve hypoxemia and hypercapnia and to treat the underlying illness and precipitating factors.

The target for treating hypoxemia is to maintain a P_aO_2 of 60 mmHg so that oxyhemoglobin saturation is maintained at about 90 per cent. A further increase in P_aO_2 does not increase the oxyhemoglobin saturation further (by virtue of falling on the flat part of the oxygen dissociation curve). An increase in FIO_2 has the dual hazards of 'oxygen toxicity' as well as of removing the 'hypoxic' stimulus to respiration; removal of this stimulus can be dangerous in subjects with chronic obstructive airway disease.

Depending on the severity of illness and the degree of hypoxemia, oxygen may be initially administered with a nasal cannula (FIO_2 uncertain) or a Ventimask (FIO_2 available at 24, 28, 31, 35, 40 and 50%). When a nasal cannula is used it must be remembered that room air is also 'entrained' along with oxygen and patients with high minute ventilations entrain more room air, thus diluting the oxygen source and thereby lowering the FIO_2. A Ventimask is less comfortable but provides a controlled FIO_2.

If the target P_aO_2 cannot be achieved without the use of an FIO_2 less than 0.6, or if the exposure to such concentrations has exceeded 48 hours, or if adequate oxygenation is associated with an unacceptable degree of hypercapnia and respiratory acidosis, intubation and mechanical ventilation are indicated.

In subjects with ARDS, an improvement in oxygenation can be attained by additional use of '*positive end expiratory pressure*' (PEEP). In this disorder the terminal respiratory units tend to collapse at low airway pressures. Positive end expiratory pressure keeps these units from collapsing, thereby improving oxygenation and V/Q match. This usually allows the FIO_2 to be lowered. PEEP is generally added in 3–5cmH_2O increments until adequate oxygenation is obtained with an FIO_2 less than 0.5. It should be remembered that though PEEP improves overall lung compliance, it may reduce cardiac output by decreasing venous return and by decreasing left ventricular compliance.

For ventilatory respiratory failure the most effective manner of treating is intubation and mechanical ventilation.

Adjuvant therapy is very important in acute respiratory failure. This includes humidification of inspired gases, clearing secretions by deep breathing, coughing, suctioning and chest physiotherapy. Infections are to be treated with appropriate antibiotics and fluid balance should be maintained carefully.

KEY CONCEPTS

Chronic obstructive airway disease

- The group includes chronic bronchitis, emphysema and asthmatic bronchitis. These disorders are characterised by chronic cough, expectoration, dyspnea, and a reduction in FEV_1(FEV_1/VC<60%) which is not reversible with pharmacologic agents. Risk factors for COPD include smoking, age, male sex, and increased pulmonary proteolytic activity (as in α_1-antitrypsin deficiency).
- Chronic bronchitis patients (*blue bloaters*) complain of a chronic cough with expectoration and wheezing. There is a reduction of FEV_1 but the diffusion capacity is normal. Emphysema patients (*pink puffers*) present with dyspnea, reduced FEV_1 and diffusion capacity and a *barrel chest*. Complications include respiratory failure, intercurrent infections and cor pulmonale.
- The response of FEV_1 to bronchodilators is of prognostic value. Chest X-rays reveal flat diaphragms with hyperinflated lungs with a loss of vascularity.
- Treatment includes smoking cessation, oral antibiotics for intercurrent infection and inhaled bronchodilators (β_2 agonists, anticholinergics, methylxanthines); corticosteroids may be helpful in treating acute exacerbations. Nocturnal O_2 delivery improves survival and the quality of life in patients with severe hypoxemia. Pulmonary rehabilitation (exercise training) is also helpful. Consider administering vaccines against pneumococci and influenza.

Bronchial asthma

- Bronchial asthma is the *reversible* narrowing of airways along with airway *inflammation* and bronchial *hyper-responsiveness*. It could be *extrinsic atopic* (IgE-mediated, family history of atopy and positive bronchial challenge tests), *extrinsic non-atopic* (occupational pollutants, mediated by non-IgE mechanisms) or *intrinsic* (older patients, no atopy, increased blood/ sputum eosinophils).
- The clinical hallmark is wheezing attacks characterised by tachypnea and the use of accessory respiratory muscles. Auscultation of lung fields reveals expiratory rhonchi. Cyanosis and pulsus paradoxus are indicators of severe airway obstruction.
- ABG analysis is vital for evaluating the extent of hypoxemia/hypercapnia and for assessing the severity of an asthmatic attack. PEFR, FEV_1 are also important measures for assessing the severity of airway obstruction and monitoring the response to bronchodilators. A value of FEV_1<25% (of that predicted for age, height and sex) is an indication for hospitalisation.
- Treatment includes β_2 agonists (aerosolised [via metered dose inhalers or nebulisers] or systemic administration). Anticholinergics and methylxanthines are useful therapeutic adjuncts; a short course of high dose corticosteroids may be used. Sodium cromoglycate may be useful for prophylaxis of attacks.

Respiratory failure

- Respiratory failure (defined as P_aO_2<50 mmHg, with or without hypercapnia [P_aCO_2> 45 mmHg]) may be due to *oxygenation failure* (*Type I*) or due to ventilatory failure (*Type II*).
- Oxygenation failure (impaired intrapulmonary gas exchange) results in *hypoxemia* and may be due to decreased FIO_2 (e.g. high altitude), hypoventilation, impaired diffusion (e.g. interstitial lung disease, emphysema), V/Q mismatch (e.g. airways obstruction, consolidation, edema) or an intrapulmonary shunt (diffuse pulmonary disease).
- Ventilatory failure (impaired movement of gases between the atmosphere and the lungs) results in *hypercapnia*. It may be due to decreased respiratory drive (central mechanisms, such as the use of sedatives, hypothyroidism), increased work load (e.g. restrictive lung disease, airway obstruction), or impaired respiratory muscle strength.
- Arterial blood gas analysis is vital for planning management strategies. Oxygenation failure is treated with increase in FIO_2, with the use of PEEP to recruit alveoli, and by providing support for cardiac function. Ventilatory failure is treated by removing any underlying cause, and by providing mechanical ventilation where and when appropriate.
- Supportive measures include clearing of respiratory secretions, humidification of inspired air, administration of antibiotics to combat infections, and correction of any electrolyte and fluid imbalances.

Adult respiratory distress syndrome

- ARDS (wet lungs) is initiated by any cause of diffuse lung injury that damages the capillary endothelium or the alveolar epithelium.
- ARDS is a form of *non-cardiogenic pulmonary edema* (increased capillary permeability with normal pulmonary wedge pressures). The pathophysiologic abnormalities include ventilation-perfusion imbalance with intrapulmonary shunting of blood and stiff non-compliant lungs.
- Causes of ARDS include aspiration, sepsis, inhalation injury, pancreatitis, trauma, fat embolism, and drug-induced pulmonary injury.
- Its clinical presentation is with acute respiratory distress (tachypnea) 24–48 hours after the initiating insult, accompanied by hypoxemia, hypocapnia and a perihilar haze on the chest X-ray.
- Treatment of ARDS is directed at correcting pulmonary injury, and towards improving oxygenation (maintaining P_aO_2 between 60–80 mmHg) with intubation, PEEP, or with mechanical ventilation. Supportive measures include antibiotics for infections. Mortality is related to the age of the patient and the severity of lung injury.

11.5 Interstitial lung disease

The term *interstitial lung disease* encompasses a heterogeneous group of over a hundred entities which share the roentgenologic appearance of diffuse interstitial opacities and the clinical symptomatology of progressive dyspnea.

Epidemiology In roughly, a third of cases of interstitial lung disease, an etiologic agent has been implicated. Clusters of cases are found with occupational exposure to inorganic dust. The leakage of methyl isocyanate gas into an urban area of Bhopal (India) in 1984 has led to interstitial lung disease in a large number of residents there. The common causes are listed in Table 11.13.

Table 11.13 Causes of interstitial lung disease

1. Idiopathic (fibrosing alveolitis)
2. Pneumoconiosis
   - coal worker's pneumoconiosis
   - silicosis
   - asbestosis
   - berylliosis
3. Hypersensitivity pneumonitis (Extrinsic allergic alveolitis)
   - farmer's lung
   - bird fancier's lung
   - bagassosis
4. Drug-induced
   - hypersensitivity (nitrofurantoin, amiodarone, salazopyrin)
   - cytotoxic damage (busulphan, bleomycin)
5. Immunoinflammatory disease
   - rheumatoid arthritis
   - progressive systemic sclerosis
   - Wegener's granulomatosis
   - Goodpasture syndrome
6. Miscellaneous
   - sarcoidosis
   - eosinophilic granuloma
   - ideopathic pulmonary hemosiderosis
   - neurofibromatosis
   - tuberous sclerosis
   - radiation injury

Etiopathogenesis The interstitial lung diseases share the common pathogenetic sequence of *injury → alveolitis → fibrosis → endstage pulmonary disease*. The injurious agents may reach the lung by inhalation or by circulation and may injure the lung by a direct toxic effect or by indirect means mediated by free radicals, eicosanoids and other inflammatory mediators.

The initial stage in the disease is injury which provokes a local cellular and humoral immune response resulting in the accumulation of lymphocytes and local production of immunoglobulins (IgG and G3). Release of cytokines (interferon) and local production of immune complexes activate the alveolar macrophage to produce chemotactic factors for the polymorphonuclear leucocytes. This stage of *alveolitis* is characterised by interstitial neutrophils and lymphocytes and a mild increase in fibroblasts. The next stage is stimulation of a growth of a clone of fibroblasts that proliferate in response to growth factors produced by the alveolar macrophage. Three such stimulators are

a 440,000 dalton glycoprotein called *fibronectin* (normally a component of the extracellular matrix and having fibroblast binding domains), the *AMDGF* (18,000 dalton protein, called the alveolar macrophage derived growth factor) and the *PDGF* (29,000–33,000 dalton dimeric glycoprotein called platelet derived growth factor). Fibronectin and PDGF are *competence factors,* that is, they help in the early stage of G1 phase of mitosis, and AMDGF is a *progression factor* that helps in later stages of G1 phase of mitosis of the fibroblasts. The proliferating clone of fibroblasts differs in the type of collagen it produces; an increase in Type I/Type III collagen ratio in the lung interstitium results. Soon the fibroblast becomes the dominant cell in the interstitium and severe fibrosis results.

Pathophysiology Interstitial lung disease is characterised by a reduction in vital lung capacity that correlates well with a reduction of total lung capacity and a decreased lung compliance. There is no major airway obstruction but interestingly 70 per cent of patients show evidence of small airway obstruction that is possibly related to inflammation and granulomas in these airways. The pathophysiologic hallmark is, however, *hypoxemia.* The resting arterial hypoxemia in early stages is mild with a PO_2 of 60–80 mmHg. This is related to a fall in DL_{CO} (diffusion capacity) that is about half that predicted. This increase in DL_{CO} is due to an altered diffusability of the pulmonary membrane (D_m); the other component of diffusion capacity, that is, pulmonary capillary blood volume (QV_c), is normal. Exercise exacerbates the hypoxemia and in early stages, exercise-induced cyanosis may be observed. With exercise, the transit time of a red blood cell across the pulmonary capillaries diminishes significantly to less than 0.5 seconds and the increased thickness of the alveolar membrane further hampers the diffusion and equilibration of gases.

An increased load of breathing with a marked increase in minute ventilation (at rest and while exercising) is also seen in these patients. This is due to a preferential increase in the respiratory rate rather than the tidal volume which is presumably mediated by an excess afferent stimulation of the respiratory centres by stretch/J receptors in the lung parenchyma which get enmeshed in the fibrous tissue. It may also be due to an inappropriate length-tension relationship of muscle spindles within the muscles of the chest wall. The increased respiratory rate combines with the decrease in lung compliance and the increased physiologic dead space to increase the work of breathing threefold as compared to normal individuals.

Clinical features Interstitial lung disease affects more males than females and is more common in the fifth decade of life. Dyspnea is the commonest symptom and tachypnea the commonest sign. A flu-like onset with fever and arthralgias-myalgias has been reported with idiopathic pulmonary fibrosis. Hypersensitivity pneumonitis and drug-induced lung disease may have an associated non-productive cough and fever with chills, thus mimicking an infectious pneumonia. Hemoptysis is rare and suggests the diagnosis of pulmonary vasculitis or one of the pulmonary hemorrhage syndromes. Chest pain may be seen with pleural involvement, as in collagen vascular diseases; in such cases the manifestations of the primary disorder often dominate the clinical picture.

Physical examination may reveal clubbing but a hypertrophic osteoarthropathy is so rare that it should prompt a search for an underlying neoplasm. Examination of the chest may reveal retraction and decreased chest wall excursion of the side with pulmonary fibrosis. There may be a tracheal shift to the side of the more fibrosed lung (if it is asymmetrical) and an impaired note on percussion. Auscultation of the lung fields reveals mid to late inspiratory crackles known as *velcro rales.*[1] Wheezing and rhonchi are rare. With advanced diseases, signs of pulmonary

[1] Like the opening of a velcro fastener

hypertension develop, with accentuation of the pulmonic component of the second heart sound on cardiac auscultation and appearance of a parasternal heave on palpation. Eventually clinically evident cor pulmonale with right-sided cardiac failure develops.

Investigations A comprehensive indepth history is essential in every case of interstitial lung disease. A history of occupational exposure to inorganic or organic dusts is important; however, in many cases the source of the culprit antigen may not be clear. A history of drugs used as medication must be obtained.

A chest roentgenogram is important to assess the extent of the disease process although it may be deceptively normal in a tenth of patients. The radiographic abnormalities may be grouped into four patterns. The *acinar pattern* is characterised by multiple opacities with indistinct margins, occasionally seen with air bronchograms and sometimes, when coalescent, having a ground glass appearance. The *nodular pattern* with discrete punctate nodules is seen in Wegener granulomatosis and lymphomatoid granulomatosis. The *reticular pattern* consists of fine to coarse curvilinear densities of variable size. The *reticulonodular* or *mixed pattern* is the commonest and involves a combination of the above patterns. With endstage lung disease, cystic changes appear leading to a honey combed appearance on the X-ray. Hilar adenopathy suggests sarcoidosis, berylliosis or silicosis, the latter especially if there is egg shell calcification of the nodes. Pleural plaque-like calcification suggests absestosis. Silicosis, ankylosing spondylitis and sarcoidosis preferentially affect the upper lobe, though the whole lung may be involved. Predominant involvement of the lower lung fields is seen in asbestosis, idiopathic pulmonary fibrosis, collagen vascular disease and drug-induced pulmonary fibrosis.

Pulmonary function tests are required to establish and quantify the restrictive pathophysiology so as to serve as a baseline for further follow-up with treatment. Ancillary laboratory studies are useful if the index of suspicion is high for a particular disorder; thus, the serologic presence of antinuclear antibodies for systemic lupus erythematosus, or serum precipitins to microbial antigens (hypersensitivity pneumonitis) may be looked for.

Fibreoptic bronchoscopy with transbronchial biopsy is usually essential for ruling out infection, and for establishing the diagnosis of specific diseases such as sarcoidosis, inorganic dust diseases, hypersensitivity pneumonitis, and Langerhans cell granulomatosis. The role of bronchoalveolar lavage (BAL) for monitoring therapy is controversial. An elevated lymphocyte count along with high phospholipids in the BAL fluid have been said to predict a steroid response and a recurrence of abnormal BAL cell counts may presage a deterioration. An excess of eosinophils in the BAL fluid is said to predict a response to cytotoxic drugs. Other workers have questioned the value of periodic BAL for disease monitoring. Gallium ^{67} lung scans have also not been found to be useful for monitoring the disease activity.

If the diagnosis is still not established after bronchoscopic biopsy, an *open lung biopsy* may be contemplated, selecting a region with average involvement on the X-ray (a severely involved area may just reveal dense fibrosis). The decision for open lung biopsy, however, must be individualised.

Treatment The initial step is to *identify any injurious agent* and to remove the patient from the offending environment. The next step is to *suppress the inflammatory response* in the lung parenchyma and prevent disease progression. Understandably, acute forms of the disease, such as acute organic or inorganic dust disease, acute radiation pneumonitis and drug-induced pulmonary fibrosis, are more responsive to treatment. About a third of patients with idiopathic pulmonary fibrosis have an objective response to steroids. Prednisolone is given at a dose of 1.5 mg/kg/day for 6 weeks and tapered over the next 18 weeks to 0.25 mg/kg/day.

Cyclophosphamide can also be tried at a dose of 1.5 mg/kg/day for steroid failures. Patients with idiopathic pulmonary fibrosis who respond to any therapeutic modality do so within 6 months and the benefits of therapy persist. Patients with alveolitis show the best response; no response is expected in the chronic fibrotic stage with 'honeycomb' lungs. Patients with pulmonary vasculitis may benefit from a combination of corticosteroids and cytotoxic agents, whereas additional plasmapheresis may be of benefit in patients with alveolar hemorrhage syndromes.

Newer forms of therapy which are at present investigational include colchicine, which inhibits the release of fibronectin and AMDGF from the alveolar macrophages, and aerosolised gamma interferon which inhibits the growth of dividing fibroblasts. *Unilateral lung allograft transplantation* has also been attempted with reports of an improvement in exercise tolerance post-operatively. *Combined heart-lung transplantation* can be done in endstage lung disease with cor pulmonale.

Prognostic factors The adverse prognostic factors are old age, longstanding symptoms, marked breathlessness, a lack of roentgenographic infiltrates, a non-cellular histology and a failure to respond to a trial of steroids.

KEY CONCEPTS

Interstitial pulmonary fibrosis

- IPF is an inflammatory reaction to pulmonary parenchymal injury which may be mediated by immune mechanisms (idiopathic, connective-tissue disease), occupational exposure (*pneumoconiosis*), infections, hypersensitivity reactions (*to moulds, fungi, chemicals*) and genetic factors.
- The cycle of *injury* → *alveolar fibrosis* → *injury* results in a restrictive lung physiology in IPF.
- The typical presentation is of a middle-aged patient who has exertional dyspnea and a non-productive cough. Physical examination reveals basilar end-inspiratory *velcro* crackles. Clubbing of fingers may be present. Symptoms of pulmonary hypertension with *cor pulmonale* develop eventually.
- The chest X-ray may show a *ground glass* appearance, *reticulonodular* infiltrates, or *honeycombing*. PFT reveals a restrictive physiology with a reduction of DL_{CO}; serum may show immune complexes, while BAL may reveal lymphocytosis.
- Prednisone is useful in a quarter of patients (those with a cellular infiltrate and without extensive fibrosis); if there is no response to steroids, consider using cyclophosphamide or azathioprine alone or in combination with steroids. The median survival of IPF patients is about five years. A variant which is rapidly progressive (*Hamman-Rich syndrome*) is associated with high fatality.

11.6 Lung infections

PNEUMONIA

Pneumonia is an inflammatory process of the lung parenchyma. It is usually produced by virulent microorganisms though it can result from other noxious stimuli such as fumes or gas inhalation, drug reaction, exposure to chemicals or heavy metals and radiation.

Epidemiology Pneumonias are often divided into those developing in the community (*community-acquired*) and those developing in a nosocomial environment (*hospital-acquired*). Most community-acquired pneumonias are caused by a small number of etiologic agents. The commonest agents are *Streptococcus pneumoniae* (50–80%), *Mycoplasma pneumoniae* (20–40%), *Staphylococcus aureus* (1–10%), *Hemophilus influenzae* (<5%), gram-negative bacilli (<5%) and mixed anerobes (<5%). Hospital-acquired pneumonia is usually due to anerobes and gram-negative organisms (Pseudomonas, *E. coli,* Klebsiella). Patients at highest risk are the elderly, chronically ill, debilitated individuals who are often the most immunocompromised.

Pathogenesis The infective organisms gain entry into the lung parenchyma either by inhalation into the tracheobronchial tree which is the commonest mode or by aspiration of oropharyngeal secretions or by the bloodstream by way of the pulmonary and bronchial arterial systems. The type of pulmonary involvement is often a characteristic of the invading organism. Thus Mycoplasma tends to cause an intense tracheobronchial inflammation with a diffuse peribronchial response. Most viral organisms produce an interstitial infiltrate. The pneumococcus and other bacterial pathogens produce rapid alveolar infiltrates; the beta hemolytic streptococcus involves the pleura early and intensely leading to rapid accumulation of large pleural effusions. Organisms like *Mycobacterium tuberculosis* and fungi are usually inhaled into distal air spaces and are 'cleared' by the macrophages and transported by the lymphatics to hilar lymph nodes; hilar adenopathy is commonly observed in primary infections with these organisms. Necrotising infection is a hallmark of staphylococcus, gram-negative organisms and anerobes.

Pathology An untreated 'classical' pneumonia goes through the four pathologic phases: phase of *congestion,* phase of *red hepatisation*, phase of *grey hepatisation* and a phase of *resolution,*[1] in that order. With the advent of antibiotic treatment, early diagnosis and initiation of treatment the pulmonary parenchymal pathologic changes undergo a rapid evolution with one or more phases merging into the other.

Pathophysiology In general, a non-necrotising pneumonia produces a low V/Q zone; ventilation is reduced due to alveolar filling

[1] Hepatisation refers to a 'liver-like' solid consistency of the lung.

while perfusion is maintained. Hypoxic pulmonary vasoconstriction does reduce pulmonary flow to the affected segments. The net result is arterial hypoxemia, usually reflecting the extent of lung involvement. Associated tracheobronchitis can increase airway resistance and the work of breathing. Associated pleural involvement can also produce a reduction in ventilation. Viral pneumonias and mycoplasmal disease, that affect the lung interstitium, can result in reduction in lung volumes, reduced compliance and diffusion abnormalities. Some of these abnormalities can persist for a few weeks after the resolution of the pneumonia.

Clinical features The clinical manifestations of a typical pneumonia include an abrupt onset of shaking chills (a 'single' chill in the case of pneumococcus), high grade pyrexia, pleuritic chest pain and a productive cough with a purulent, occasionally blood-streaked (rusty), sputum. The patient appears acutely ill, and tachypneic, and physical examination reveals signs of a 'consolidation'. Nosocomial pneumonias often have a more insidious course. The features of 'atypical' pneumonias are described later.

It should be stressed that many organisms that are supposed to behave in a classical fashion do not do so in a given patient. Conversely many patients have a modified course of pneumonia due to certain characteristics.

Investigations A summary of diagnostic investigations is provided in Table 11.14. The choice of an investigation is guided by its risk-utility ratio. In a severely ill patient a definitive result is rapidly required, thereby providing a greater justification for taking a risk.

Treatment Empirical selection of therapy at onset is often essential. Once a rational diagnostic plan is formulated, therapy does not hinder the diagnosis. Therapy can be tailored to the infective organisms once the bacteriologic diagnostic procedures yield clues. In general, erythromycin (500 mg qid for 10 days) is the treatment of choice for community acquired pneumonia with an excellent spectrum of activity which includes activity against Pneumococcus, Staphylococcus, Mycoploasma and Legionella. Treatment of infection due to individual agents is detailed in the section on infections.

Recurrent Pneumonia

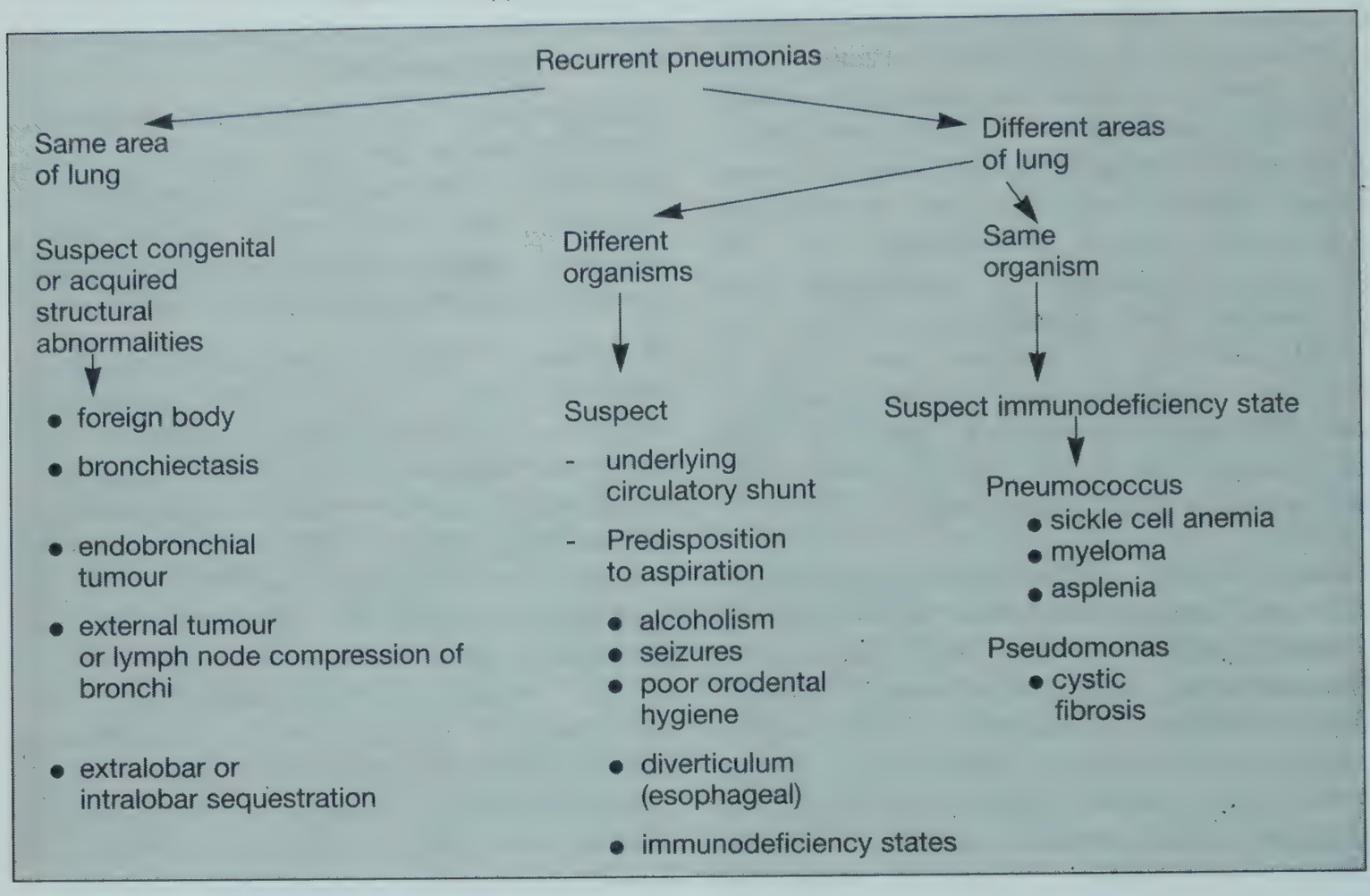
An algorithmic approach to the patient with recurrent attacks of pneumonitis is provided in Table 11.15.

Table 11.14 Diagnostic procedures in pneumonia

A. Low invasion-low risk (not definitive)	Blood counts Check X-ray Skin tests
B. Low invasion-low risk (may be definitive)	Sputum smear and culture Blood culture Urine culture Serology (for unusual organisms) PCR* - sputum
C. High invasion-high risk (may be definitive)	Transtracheal aspiration Pleural tap/Biopsy Bronchoscopy (aspiration, brushing, BAL, biopsy) Direct needle aspiration (percutaneous)

* PCR : Polymerase chain reaction

Table 11.15 Approach to a patient with recurrent pneumonias



Atypical Pneumonia

The term atypical pneumonia refers to the clinical syndrome of pneumonitis with fever but with an absence of shaking chills, toxemia, pleural pain or rusty sputum. The white blood cell count is typically normal and there is no demonstrable bacterial pathogen on a Gram stain of the sputum. Mycoplasmal pneumonia is the most common cause of a typical pneumonia. Legionella, Coxiella and viral pneumonias also present often with atypical features.

Other features Table 11.16 provides a detailed comparison of the clinical features of the common 'atypical' pneumonias.

LUNG ABSCESS

A lung abscess is a localised collection of pus in the lung. The definition implies the occurrence within the lung parenchyma of both necrosis and suppuration. Whereas the above definition serves the pathologist well, clinically speaking a lung abscess is a roentgenologic diagnosis, that is, it is the presence of a cavity with a well-defined wall on the chest X-ray. Strictly speaking, therefore, even tubercular and fungal cavities are lung abscesses. The discussion in this chapter is, however, confined to pyogenic lung abscesses.

Epidemiology Lung abscesses are most often related to aspiration and a resultant anerobic necrotising pneumonitis. The commonest organisms are Peptostreptococcus, Fusobacterium and, on occasion, the Bacteroides species. They may also occur as a post-pneumonic complication, *Staphylococcus aureus* being a common pathogen. Lung abcesses may also be multiple due to a pyemic process. Such abscesses result after pelvic sepsis or may be

Table 11.16 Comparison of typical and atypical pneumonias

	Typical	*Atypical*		
	Pneumococcal pneumonia	**Legionnaire's disease**	**Mycoplasma pneumonia**	**Influenza pneumonia**
Source	human	non-human; contaminated aerosols	human	human
Age	>30 yrs	adults	young adults	<5 yrs, >65 yrs
Season	winter	summer	winter	winter
Underlying disease	common	very common	rare	very common
Incubation period	–	2–10 days	2–3 weeks	1–5 days
Onset	acute, single chills	acute to subacute, multiple chills	gradual	subacute
Pleural involvement	common	common	rare	rare
Sputum	purulent, rusty	purulent or mucoid	mucoid	mucoid
Leukocytosis	common	common	uncommon	uncommon
X-ray	lobar consolidation	early consolidation, rapid progression, prolonged resolution	patchy, hilar adenopathy	broncho-pneumonia
Clinical–radiologic discrepancy	unusual	may exist	common*	common*
Extrapulmonary features	uncommon herpes labialis	GI, CNS, renal	GI, bullous myringitis	cardiac, CNS, hepatic
Other laboratory findings	positive blood culture, positive Gram stain	hyponatremia, abnormal liver and renal function tests	cold agglutinins	non-specific
Treatment	penicillin G or erythromycin	erythromycin or tetracycline / ciprofloxacin	erythromycin or tetracycline	amantadine for Type A

* Patient looks better than the X-ray would suggest. In pneumocystis pneumonia, the patient looks very sick, X-ray findings being sparse.

related to right-sided endocarditis. Fungal organisms may produce lung abscesses in diabetics, drug addicts and the immunosuppressed. An amebic liver abscess can rupture across the diaphragm resulting in pleuropulmonary amebiasis. A lung abscess can be a feature of such an infection.

Etiopathogenesis The hallmark of a lung abscess is a *necrotising pneumonitis*. Every abscess begins with an infection by a pyogenic organism that has a propensity for causing tissue necrosis. Such organisms include *S. aureus, K. pneumoniae*, other enteric gram-negative bacilli and anerobes. The organism

causes a central area of necrosis and the host response is characterised by a rim of surrounding polymorphonuclear leukocytes, which in turn are surrounded, with increasing chronicity of inflammation, by a collagenous wall produced by the fibroblasts. The latter wall is the capsule of the abscess and is responsible for the radiologic appearance. This process may take 7–14 days.

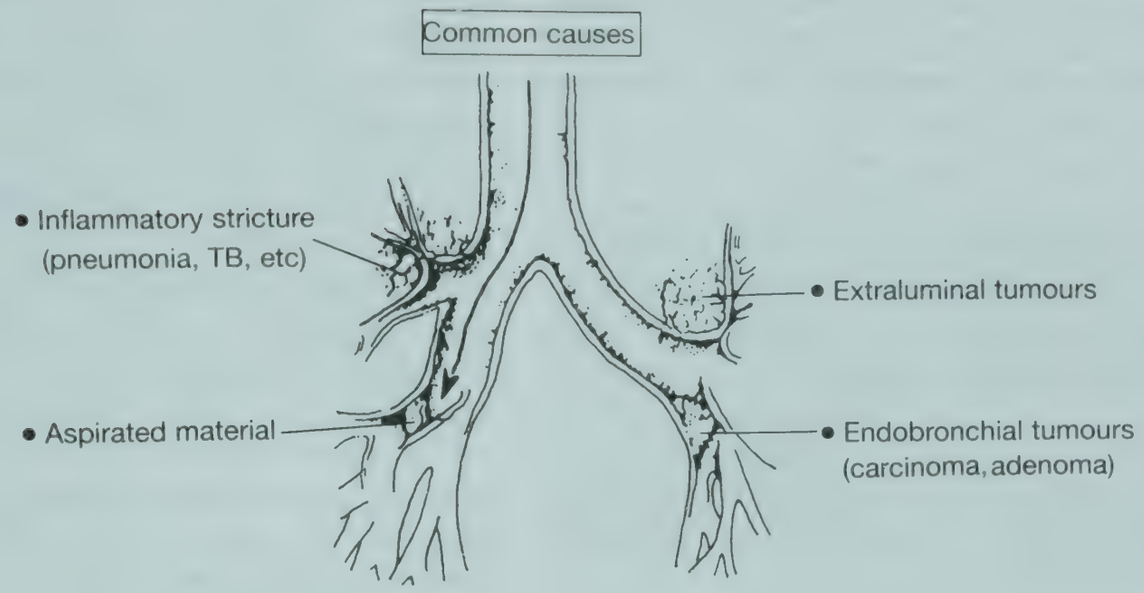
About three-fourths of all lung abscesses are related to aspiration of the oropharyngeal contents. It has been shown in experiments that about 50 per cent of conscious people and 70 per cent of unconscious patients aspirate oropharyngeal secretions at night. The effective host defences constituted by the cough reflex, the mucociliary clearance mechanisms and the submucosal leukocytes clear these secretions and the constituent organisms. Even the aspiration of 0.01 ml of oropharyngeal secretions would mean aspiration of 10^6 anerobes. Thus aspiration pneumonia requires an altered state of consciousness or impaired swallowing mechanisms with a breakdown of host defence mechanisms due to conditions like alcoholism, status epilepticus, neurologic dysphagia (such as, myasthenia), mechanical dysphagia (like achalasia). Bad orodental hygiene would increase the availability of anerobes in the oral cavity. The gravity dependence and peripheral location of most abscesses is understandable since most aspiration occurs in the supine position. As the right bronchus has a less acutely angled take off, the right lung and specifically its dependent bronchopulmonary segments – the posterior segment of the upper lobe or the superior segment of the lower lobe – are the sites of predilection (Fig 11.15). When a procedure such as tonsillectomy or a tooth extraction is done in the upright position, aspiration would be preferentially into the basilar segments of the lower lobes. The bronchial 'embolus' of aspirated contents would explain the occasional subpleural location of the lesion. The necrosis tends to proceed in a pyramidal fashion towards the hila. Unlike a necrotising pneumonia, pleural involvement with resultant empyema is less frequent with lung abscesses.

Other potential complications include massive hemoptysis due to erosion of a vessel in its wall, metastatic abscesses and contiguous spread to the pericardium. About a fourth of all lung abscesses are related to pyogenic necrotising pneumonias. An abscess is said to be chronic if it is of a duration greater than six weeks. The various causes of a lung abscess are shown in the Fig 11.15.

Clinical features The most common history is one of a productive cough with putrid sputum, which may occasionally be blood-tinged. The usual duration of symptoms in most patients is more than a week (an average of 12 days). Fever, pleuritic chest pain and malaise are very common. A condition predisposing to aspiration, such as poor periodontal hygiene, may be evident.

Physical examination discloses fever (commonly 102°C) and, occasionally, clubbing. Localised *amphoric* or *cavernous* breath sounds with rales suggest a parenchymal cavity. Tympany is variable, depending on how superficially the cavity is located.

Investigations A hemogram reveals a neutrophilic leukocytosis of a variable degree and blood cultures are usually sterile. A definitive diagnosis of lung abscess is made on a chest X-ray which demonstrates a cavity. An air-fluid level indicates an inadequate communication with a bronchus. Sputum culture and smear are useful in aerobic pyogenic lung abscesses. In anerobic lung abscesses, anerobic sputum cultures may be obtained either by transtracheal or transthoracic percutaneous fine needle aspiration or by bronchoscopic aspirates. Anerobic abscesses are typically polymicrobial. Transtracheal aspiration is avoided in the presence of hypoxemia or a bleeding tendency. Transthoracic aspiration carries the risk of pneumothorax. Gas liquid chromatography has



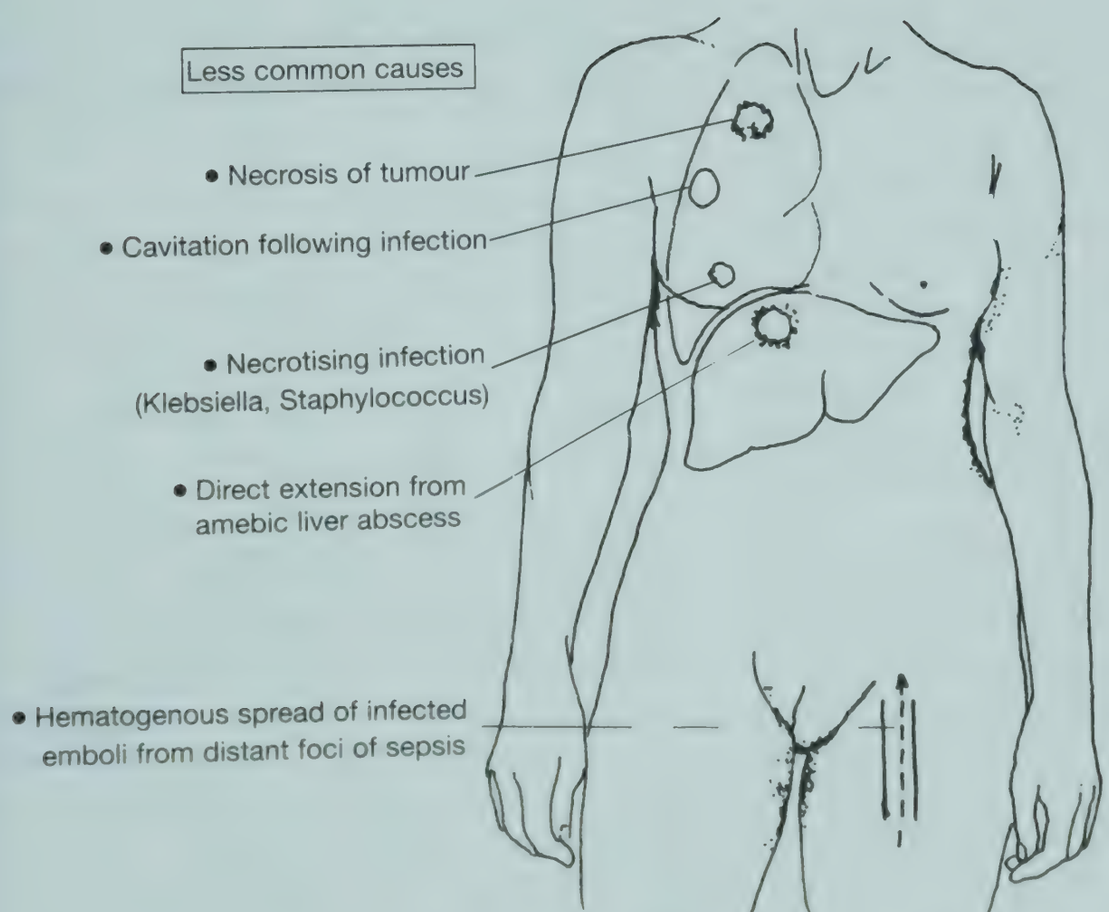


Fig 11.15 Lung abscess : possible causes

been described as a means of rapid identification (within an hour) of anerobes in expectorated sputum by detecting volatile fatty acids produced by these organisms. Most authorities however, believe that patients with putrid sputum do not require sputum culture as this observation is in itself diagnostic of an anerobic lung abscess. Culture for acid fast bacilli and fungi can be sought in non-resolving abscesses. Sputum cytology should also be obtained to rule out an underlying malignancy in such cases.

Differential diagnosis The differential diagnosis includes a cavitating malignancy, cavitary infarction and infected congenital cysts.

Treatment The dictum for treatment of any abscess anywhere in the body is suitable antibiotics and drainage. This is true of the lung abscess as well.

The importance of postural drainage and chest physiotherapy needs emphasis. The patient must sleep with the affected lung dependent to obviate aspiration into the contralateral unaffected lung (Fig 11.16). Persistence despite adequate antibiotic cover may reflect an inadequate drainage; in that case bronchoscopic drainage would be indicated.

Antibiotic choice is guided by sputum smear/culture results and clinical judgement. Aqueous penicillin G 1.5–2 million units i.v. every 4 hours is usually a satisfactory regimen. Other penicillins (other than the anti-staphylococcal agents) such as ampicillin and amoxicillin are also effective. Clindamycin is another good drug which, though expensive is as effective as penicillin; in fact it was found to be superior in one study. Experience with metronidazole alone had been poor, though it may be used in combination with penicillin G. A total duration of treatment of six weeks is recommended with a switch to oral antibiotics once there is a clinical response. Even with adequate treatment fever may persist for upto 21 days and the cavity may be present radiologically for upto 10–12 weeks. The failure of an abscess to resolve could be due to inadequate treatment

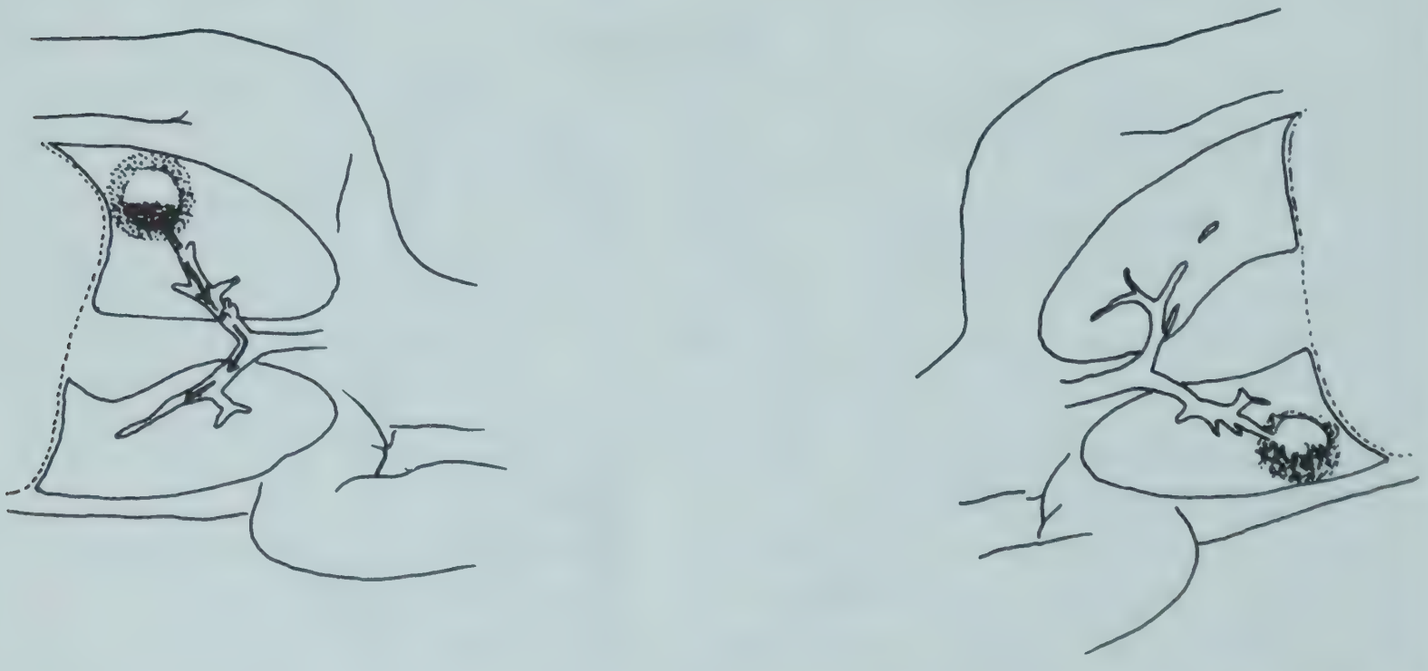


Fig 11.16 Management of lung abscess : proper postural drainage is important. Position **a** promotes spill of infected material to the contralateral healthy lung. Position **b** is recommended.

(such as improper choice of antibiotics, or an improper dosage), inadequate drainage, an unusual organism (tuberculosis or fungal), a masquerading malignancy or recurrent infection due to a persistent source of aspiration. A masquerading neoplasm must be strongly suspected if the patient is a middle aged smoker and there is evidence of an unusual location of the abscess, atelectasis, hilar adenopathy or a failure to respond to adequate antibiotic cover. In rare cases, a lobectomy may be required for a lung abscess refractory to all other treatment.

Prognosis Mortality rates for lung abscesses vary from 5 to 15 per cent. A cavity size greater than 6 cm, multiple abscesses, associated obstruction or an immunocompromised host are adverse prognostic factors.

Bronchiectasis

Bronchiectasis is defined as irreversible bronchial dilatation with suppuration. This definition is in part anatomic. An alternative term that is recognised by the clinician is *chronic bronchial sepsis,* that is, production of persistent purulent sputum. Though the terms may be used interchangeably, strictly speaking, not every patient with chronic bronchial sepsis has bronchiectasis, and vice versa.

Pathophysiology and etiology Chronic bronchial sepsis is the precursor of anatomical and structural changes. Tissue damage occurs, frequently with associated bronchial obstruction. Bronchial dilatation occurs because of increased intrabronchial pressure and tractional forces on the bronchial wall due to negative intrathoracic pressure. This leads to permanent fibrosis and dilatation. Squamous cells replace the normal ciliated epithelium, rendering mucous clearance ineffective, which further propitiates obstruction. The lower lobes are the most involved, the left lung more than the right. Depending on the morphology of the dilated bronchi, bronchiectasis may be *fusiform, varicose* or *saccular* (cystic). The causes of bronchiectasis are listed below. All the causes that are listed provide a milieu for the infection-obstruction-infection sequence.

Table 11.17 Causes of bronchiectasis

1. Postinfective
   - repeated childhood respiratory infection
   - pneumonia
   - tuberculosis
2. Bronchial obstruction
   - lymphadenopathy
   - foreign body
   - benign neoplasm
3. Allergy (allergic bronchopulmonary aspergillosis)
4. Hypogammaglobulinemia
5. Cystic fibrosis
6. Dyskinetic cilia syndrome
7. Congenital anatomic defects
   - bronchomalacia
   - bronchial cysts
   - sequestration

In cystic fibrosis the major defect is an impermeability to chloride ion within the sweat gland and the respiratory epithelium. The mucous contains inadequate amounts of water and is, therefore, thick and viscid since it has excess amounts of other mucous glycoproteins. In the dyskinetic cilia syndrome the dynein arms of the cilia are absent and this renders the mucociliary clearance mechanisms ineffective. Kartagener syndrome, the triad of sinusitis, bronchiectasis and situs inversus, is a subset of the dyskinetic cilia syndrome.

Clinical features The classical clinical picture is one characterised by a chronic, paroxysmal, putrid, purulent, profuse and postural cough. Intercurrent infections may cause fever. Other features in the history include anorexia, weight loss and hemoptysis. Clinical examination reveals finger clubbing and persistent medium to coarse (leathery) crackles over the affected lobes.

In the preantibiotic era, bronchiectasis was often complicated by metastatic abscesses, cor pulmonale, secondary amyloidosis, empyema

and bronchopleural fistulae. These complications are now infrequent due to the increased use of antibiotics and awareness of the benefits of postural drainage.

Investigations The plain chest radiographs may appear normal in the early stages of the disease. Abnormal features suggesting the diagnosis include tubular shadows (called tram lines) that denote thickened bronchial walls or cystic shadows (cystic bronchiectasis). In the pre-CT era, bronchograms were obtained to demonstrate the dilated bronchi. Today in almost all instances, CT has replaced the need for bronchography. Pulmonary function tests invariably show some evidence of airway obstruction. Sweat chloride tests or quantitative immunoglobulin studies can be obtained but only if cystic fibrosis or immunodeficiency, respectively, are suspected as diagnostic possibilities based on the clinical picture.

Management Postural drainage, chest physical therapy and antibiotics to combat intercurrent infection remain the cornerstone of therapy.

Surgery is reserved for the exceptional patient with severe localised disease and troublesome symptoms such as recurrent massive hemoptysis.

KEY CONCEPTS

- The term pneumonia is used for any inflammation of the lung parenchyma; it may be *lobar* (confined to a lobe), *lobular* (segmental), *interstitial,* or a *bronchopneumonia* (alveoli contiguous with bronchi). The majority of pneumonias are the result of bacterial infections. Mycoplasma pneumoniae is the most common cause of community-acquired pneumonia. Other common causes include pneumococcus, *Staph. aureus*, and Legionella.
- Fever with chills, production of rusty sputum, and pleuritic pain are typical complaints. Dyspnea is a prominent symptom in interstitial pneumonia. Physical findings of a consolidation include increased tactile fremitus, dullness on thoracic percussion and an area of localised bronchial breathing.
- The chest X-ray is diagnostic. In *atypical pneumonia,* clinico-radiologic discrepancy may be prominent. Leucocytosis, and positive blood cultures are useful adjuncts for diagnosis. Elevated cold agglutinin titres are seen in Mycoplasma, while serology is required for the diagnosis of Q fever.
- Oral erythromycin is the drug of choice in community-acquired pneumonia; for inpatient treatment, penicillin G is used for pneumococcus, while penicillinase-resistant penicillins are preferred for treating staphylococcal pneumonia.

Lung abscess

- A lung abscess is a collection of pus within a cavity in the lung parenchyma. It is usually the result of aspiration (it is typically polymicrobial; aspiration may be related to poor oral hygiene and to conditions associated with a diminished gag reflex), bacteremia, necrotising pulmonary infections (anerobes) or infarction, or a cavitary lung malignancy.
- Fever of 2–4 weeks duration, with production of putrid sputum is the usual presenting feature. Physical findings are those of a localised consolidation. If the abscess is large, tympany and amphoric breathing are additional physical signs. Complications include empyema, pyopneumothorax, and metastatic abscesses. The chest X-ray is diagnostic. The abscess cavity is usually located in the posterior segment of the upper lobe or the superior segment of the lower lobe; an air-fluid level indicates the presence of a bronchial communication.
- Treatment includes antibiotics (i.v. penicillin, clindamycin, followed by oral therapy) for 6–8 weeks, and postural drainage. Consider fibreoptic bronchoscopy if there is a non-resolving abscess, an atypical location or associated hilar adenopathy (to exclude an underlying malignancy).

Bronchiectasis

- Bronchiectasis refers to an irreversible anatomic widening of bronchi which is usually the result of suppuration. Causes of bronchiectasis include repeated bacterial lung infections, pulmonary tuberculosis and abnormal respiratory mucociliary clearance mechanisms (as in cystic fibrosis and dyskinetic cilia syndrome).

➢ The clinical hallmark is a *profuse, purulent* expectoration which is often *postural* (early morning). The typical physical findings are localised coarse *leathery* basilar crepitations. Complications of bronchiectasis include finger clubbing, hemoptysis, cor pulmonale and amyloidosis. Thickened bronchi may be seen on a chest X-ray (*tram track*) or in a thoracic CT scan.

➢ Treatment includes the administration of broad spectrum antibiotics for intercurrent infections, physical therapy to promote bronchial drainage and use of bronchodilators for associated bronchial obstruction. The onset of cor pulmonale may necessitate O_2 therapy. Surgery is indicated for localised resectable lesion causing recurrent massive hemoptysis.

11.7 Bronchogenic carcinoma

Epidemiology Bronchogenic carcinoma is the leading cause of death due to cancer in men and women in the USA and Europe. The disorder is more frequent in middle age with a peak incidence in the 55–65 years age group. There is a male predominance (M:F=2:1).

The single most important etiologic factor is *cigarette smoking.* Smoking results in pyrolysis of tobacco which in turn leads to pyrosynthesis of carcinogens and cocarcinogens such as benzpyrene, nitrosonicotine, β napthylamine. The risk of lung cancer is related to the amount of exposure to tar and other constituents. Thus the number of cigarettes smoked per day, the duration of the smoking habit, the age at which initiated, the depth of inhalation of smoke and the tar-nicotine content of the cigarette all seem to influence the risk of lung cancer. 'Bidis' are as harmful as cigarettes. Pipe smokers and cigar smokers are also at risk though the risk is a little less when compared to cigarette smokers. *Occupational exposure* to radiation from uranium, or radium, exposure to organic and inorganic material such as asbestos, nickel, arsenic, and beryllium also predispose a person to lung cancer. *Pulmonary scars* and fibrosis (for instance, scleroderma and diffuse interstitial fibrosis) also predispose to adenocarcinomas. Recently, dietary factors have also been implicated in the pathogenesis of lung cancer. Both smokers and non-smokers with a low dietary carotene index[1] are more likely to develop lung cancer than those with a high carotene index.

Pathology and pathobiology The development of smoking-related lung cancer represents a transition from smoking-induced atypia to smoking-induced dysplasia to a stage of *carcinoma in situ.* The cytologic appearance of bronchogenic carcinoma is varied and the WHO classification is shown in Table 11.20. The incidence, the pattern of location the rate of growth and associated pathologic features of some important subtypes are shown in Table 11.21. Table 11.19 shows the staging system used for the two main histologic types (small cell and squamous cell carcinoma).

Clinical features The clinical features of bronchogenic carcinoma (Fig 11.17) depend on whether the tumour is central and is communicating with the bronchial tree or peripheral and whether it is localised or spreading. Table 11.18 summarises the important clinical features based on local, regional and systemic spread. A fourth category of symptoms termed paraneoplastic syndromes also arise, presumably due to the release of humoral agents by some histologic subtypes.

Investigations The chest X-ray is very important for evaluation of any patient suspected to have a pulmonary malignancy. Central masses with or without hilar lymphadenopathy may suggest a squamous cell or small

[1] Carotene index is the measure of the intake of carrots and certain yellow leafy vegetables.

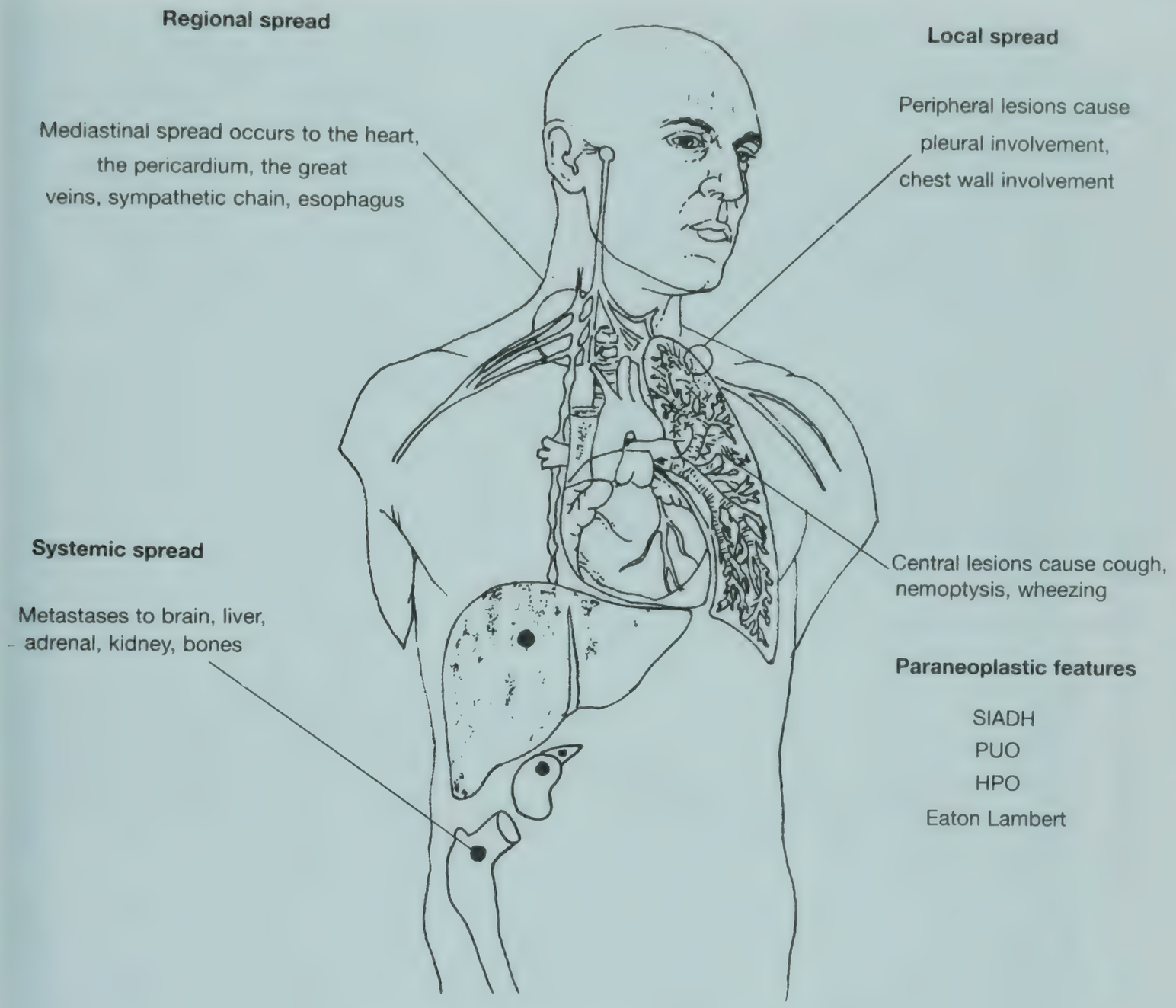


Fig 11.17 Clinical features of bronchogenic carcinoma

cell carcinoma. An isolated hilar mass or mediastinal widening is more likely in small cell carcinoma of lung. Apical tumours or tumours associated with atelectasis suggest an underlying squamous cell carcinoma. Cavitation is commonest in squamous cell carcinomas, less so in adenocarcinomas and large cell carcinomas, and is almost never seen in small cell carcinomas. Consolidation or the presence of multiple masses is rare with all the cell types. A CT scan of the lungs and the mediastinum is useful in staging lung cancer.

All patients should undergo a complete blood count, liver function tests, measurement of serum electrolytes, calcium and alkaline phosphatase that screen for hepatic and bone metastasis. Therapeutic decisions are based on a correct tissue diagnosis. The least invasive and the easiest method for obtaining a tissue diagnosis is cytological examination of the sputum. The test is highly specific but its sensitivity varies from 90 per cent for central tumours to 50 per cent for peripherally located tumours. If a pleural effusion is present, pleural

Table 11.18 Clinical features of bronchogenic carcinoma

Features due to central growth	*Features due to peripheral growth*	*Features due to regional spread*	*Features due to extrathoracic spread*	*Paraneoplastic syndrome*
• Cough - 75%, change in previous character suggestive - mucosal irritation by tumour • Hemoptysis - seen in 50%, presenting complaint in 5% - due to ulceration, vessel erosion, infection • Wheeze - intraluminal obstruction • Fever - atelectasis with post obstructive pneumonitis • Dyspnea due to atelectasis	• Chest pain - due to pleural involvement or infiltration of ribs/chest wall • Dyspnea - restrictive physiology due to parenchymal infiltration	• Dysphagia - esophageal infiltration • Hoarseness - recurrent laryngeal nerve involvement • Dyspnea - due to diaphragmatic paralysis consequent to phrenic nerve involvement • Tamponade - pericardial infiltration • Pneumothorax/ pleural effusion - pleural involvement • SVC obstruction • Shoulder pain Horner syndrome - due to brachial plexus and cervical sympathetic compression	• CNS deposits (<30%) - headache, deficits (variable) • Hepatic - anorexia - biliary obstruction - raised alkaline phosphatase • Kidneys - usually asymptomatic • Adrenal - sudden death - 50% deposits are occult	• Fever (20%) ENDOCRINE • Hypercalcemia - secretion of PTH, PGE • SIADH (secretion of ADH) • Thyrotoxicosis (secretion of TSH) • Hypoglycemia - secretion of insulin-like products • HEMATOLOGIC anemia, leukemoid reaction, venous thrombosis • NEUROLOGIC - cerebellar degeneration - polymyositis - Eaton-Lambert syndrome • DERMATOLOGIC - acanthosis nigricans - hypertrichosis • SKELETAL - hypertrophic pulmonary osteoarthropathy

Table 11.19 Staging of bronchogenic carcinoma

Non-small cell	*Small cell*
Stage I Tumour of any size confined to one lung, not involving lymph nodes or extrathoracic tissue	**Limited disease** Tumour confined to one hemithorax and/or ipsilateral supraclavicular lymph node
Stage II Tumour of any size with at least one bronchopulmonary or hilar lymph node involvement, no extrathoracic spread	**Extensive disease** Any tumour with spread more than in limited disease (above)
Stage III • Lesions not involving carina and only ipsilateral lymph node involvement • Lesions invoving carina or with contralateral spread	
Stage IV Lesions with extrathoracic spread	

Table 11.20 Pathological classification of bronchogenic carcinoma (WHO)

1. Epidermoid carcinoma
2. Small cell carcinoma
   - polygonal
   - fusiform
   - oat cell-like
3. Adenocarcinoma
   - bronchogenic
   - - acinar
   - - papillary
   - bronchoalveolar
4. Large cell carcinoma
   - solid cell (with and without mucin)
   - giant cell
   - clear cell
5. Combined epidermoid and adenocarcinoma
6. Carcinoid
7. Bronchial gland carcinoma
   - cylindroma
   - mucoepidermoid
8. Miscellaneous
   - mesothelioma
   - melanoma
   - sarcoma

fluid cytology or a pleural biopsy can be obtained. While pleural biopsy and cytology individually have a diagnostic yield of about 50 per cent, the two techniques when combined have a diagnostic yield of about 80 per cent.

Radionuclide scans are not indicated in the absence of symptoms to detect occult visceral metastases. If symptoms pertaining to a system are present, radionuclide scans can be obtained, (for example, bone scans can be ordered in a patient with skeletal pain). The exception to this rule is scanning of the CNS in patients with small cell carcinoma– with CT scan for suspected supratentorial lesions, or with MRI for suspected infratentorial lesions. Given the excellent prognosis with excision of solitary metastatic CNS nodules in patients with small cell carcinoma, CNS screening has been recommended as a routine in this histologic subtype alone (Table 11.21).

Treatment of non-small cell carcinoma

A. Treatment of non-disseminated disease

Surgery is the treatment of choice for stage I and II disease. Lobectomy yields better results than pneumonectomy. A conservative resection can

be attempted in in situ cases (carcinoma with a positive cytopathology for malignancy but with no lesion on the chest roentgenogram). Poor physiologic staging (FEV_1 <1 litre, cor pulmonale, myocardial infarction in the previous 3 months) is a contraindication for surgery. Under these circumstances radiotherapy, 5500–6000 rads as a split course or a continuous fraction, is an alternative. The Pancoast tumour (superior sulcus tumour) is treated with combined surgery and radiotherapy.

B. Treatment of disseminated disease

Widespread metastatic disease is treated with palliative radiotherapy of 2000 rads over 2–4 weeks. This diminishes symptoms such as bone pain, caval obstruction and hemoptysis. Dexamethasone has been used for intracranial metastases with compressive symptoms.

Treatment of small cell carcinoma Chemotherapy is the mainstay of therapy in small-cell carcinoma. Combination regimens employing three or four agents are used, courses being given at four-weekly intervals or in four to six cycles. The drugs used are cyclophosphamide, doxorubicin, vincristine, etoposide and cisplatinum. Newer agents with considerable promise include ifosfamide, a cyclophosphamide analogue, carboplatin, a cisplatin analogue, and teniposide, an etoposide analogue.

Radiotherapy is useful in limited stage disease to decrease local relapse rates after chemotherapy. Younger patients with limited disease and a complete response to initial chemotherapy are candidates for prophylactic cranial irradiation to reduce the frequency of CNS relapse. Less then 5 per cent of patients are candidates for surgical tumour resection.

With combination chemotherapy and radiotherapy, median survival is fifteen months for limited disease and nine months for extensive disease.

Prevention of lung cancer The most important strategy in the treatment of lung cancer is primary prevention. The majority of lung cancer deaths may be attributed to smoking. There is evidence from western countries that effective national antismoking campaigns reduce tobacco consumption and this in turn leads to a fall in incidence rates of lung cancer.

Table 11.21 Characteristics of main histologic subtypes of bronchogenic carcinoma

Cell type	*Incidence (% of all lung cancers)*	*Location*	*Pattern of spread*	*Relationship to smoking*	*Histopathologic correlates*	*Chest X-ray*	*Doubling time*
Squamous cell carcinoma	30–35	central	local invasion, lymphatic involvement	++	Keratin pearls, intercellular bridges	central with hilar involvement, cavitation+	90 days
Adeno-carcinoma	30–35	peripheral	hemato-genous, early	–	gland formation	peripheral lesion, cavitation+	180 days
Small cell carcinoma	20-25	central	hemato-genous, early	+	derived from Kulchitsky cell (lymphocyte-like but nearly double the size)	central with hilar involvement, cavitation–	30 days
Large cell carcinoma	15–20	peripheral	hemato-genous	–	poorly differentiated	peripheral	30 days

KEY CONCEPTS

Lung cancer

- Lung cancer is the most common cancer in men and women worldwide.
- Lung cancer may be *small cell type* (oat cell cancer, hilar location with predominantly blood-borne metastases), *non-small cell type* (squamous cell cancer; central location with lymphatic spread), an *adenocarcinoma* (peripheral location; may arise within scars) or on *alveolar cell carcinoma* (multifocal origin within airspaces).
- Important risk factors include cigarette smoking, exposure to asbestos, uranium and other industrial toxins (such as nickel, chromium, bischloromethyl ether).
- A lung cancer may present with *pulmonary symptoms,* with *symptoms related to intrathoracic spread* or may be associated with *paraneoplastic manifestations.* Pulmonary manifestations include cough (or change in character of a previous cough), hemoptysis, pneumonitis, atelectasis, or pleural effusion. *Bronchorrhea* is a feature of alveolar cell carcinoma. Intrathoracic spread may lead to superior vena cava obstruction, Horner syndrome (cervical sympathetic invasion), pericardial effusion with tamponade, or hoarseness (recurrent larynegeal nerve involvement). A *Pancoast* tumour (superior sulcus tumour) may invade the brachial plexus. Paraneoplastic manifestations include hypertrophic osteoarthropathy, cerebellar ataxia, Eaton-Lambert syndrome, SIADH, and hypercalcemia.
- An X-ray may reveal a peripheral or central mass lesion; there may be associated localised atelectasis or a pleural effusion. Diagnosis may be confirmed with sputum cytology or by examining fibreoptic bronchoscopic washings, brushings or biopsy.
- Treatment depends on the *histologic subtype* of lung cancer and the extent of disease spread. Localised small cell cancer is treated with a combination of chemotherapy and radiation. Extensive disease due to small cell cancer is treated with combination chemotherapy alone. Stages I and II of non-small cell cancer are amenable to surgical resection. The treatment of advanced non-small cell cancer consists of palliative measures (such as analgesics for pain). Radiation is useful in controlling bone pain, SVC obstruction, spinal cord compression or cerebral metastases. The Pancoast tumour is radiosensitive. The overall five year survival is <10%.

11.8 Diseases of the pleura and mediastinum

DISEASES OF THE PLEURA

Basic physiology The lungs are invested in a serous membrane of mesodermal origin known as the *visceral pleura.* The *parietal pleura* is another serous membrane, also of similar origin, that lines the parietes that is, the ribs and the diaphragm. The two layers of the pleura enclose a potential space, the pleural space, and are contiguous at the hilum where they form the *pulmonary ligament.* The parietal pleura is innervated by intercostal nerves and the phrenic nerve. The latter innervates the diaphragmatic pleura. The parietal pleura obtains its vascular supply from systemic capillaries and is drained by the systemic veins. The visceral pleura lacks pain fibres, is supplied by pulmonary capillaries and drains into the pulmonary veins.

The pleural space normally has about 5–25 ml of pleural fluid. It was believed in the past that the pleural fluid is filtered at the parietal pleura from systemic capillaries (at a vascular pressure of about 30 cmH_2O) and reabsorbed at the visceral pleural surface by pulmonary capillaries (at a vascular pressure of about 11 cmH_2O) in accordance with Starling's principles for transcapillary exchange. Recent evidence, however, suggests that the major exit pathway of pleural fluid is not the visceral pleura but the dilated lacunar portions of the lymphatics of the parietal pleura. These lacunar portions are called the *stoma* and are unique to the parietal pleura. It is currently believed that the rate of pleural fluid resorption is about 0.1 ml/kg/hour per day and not several litres as was earlier believed.

Pleural Effusions

Pathophysiology An increase in the amount of pleural fluid that is normally present due to accumulation of fluid of a similar or dissimilar constitution is defined as a pleural effusion. Effusions may arise due to an increased entry of pleural fluid as a result of increased capillary hydrostatic pressure (as in congestive heart failure), or an increased permeability (as in pleural inflammation), or a decreased capillary oncotic pressure (as in cirrhosis or nephrotic syndrome).

Pleural fluids may be *exudates* or *transudates.* An exudate pleural fluid has one of the following features:

a) $\frac{\text{pleural fluid protein}}{\text{serum protein}} > 0.5$

b) $\frac{\text{pleural fluid LDH}}{\text{serum LDH}} > 0.6$

c) pleural fluid LDH > 200 iu (or more than two-thirds of the normal) or

d) pleural fluid protein > 3 g/dl.

A transudate has none of these features.

Exudates are further classified as *simple* exudates and *complicated* (parapneumonic) exudates. A complicated exudate has one of the following characteristics:

a) pH below 7

b) pH 7–7.2 with LDH > 1000 iu/l

c) glucose level < 40 mg/dl

d) a positive gram-stain for microorganisms

The causes of pleural effusion are summarised in Table 11.22.

Clinical features The symptoms of a pleural effusion include pleuritic chest pain usually localised to the site of pleural irritation, except central diaphragmatic pleural pain that is felt as referred shoulder pain. A heaviness of the chest may be felt and the patient may be breathless due to diminished lung volumes consequent to compression of the lung parenchyma by pleural fluid. Cough is an associated symptom which is not well understood but could possibly be related to compression of the bronchial walls, or due to associated parenchymal disease.

Physical findings depend on the amount of pleural fluid. A large effusion is associated with decreased movement of the hemithorax, bulging of intercostal spaces on the affected side, and a contralateral shift of the trachea. Palpation reveals a diminished or absent tactile fremitus and the hemithorax is dull on percussion. Breath sounds are diminished on the affected side though on occasion they may be accentuated with a 'bleating' quality (*egophony*) just above the effusion.

Investigations The standard PA chest film can detect pleural fluid only when about 250 ml of fluid has collected and this is evident as a blunting of the costophrenic angles. Small amounts of fluid (15–25 ml) are detected by a lateral decubitus film when a separation of more than 1 cm of outer chest wall from the lung parenchyma on the dependent side suggests the diagnosis.

As pleural fluid accumulates in larger amounts the '*meniscus sign*' (that is, the rising level in the axilla in a chest PA film) appears. Subpulmonic effusions can simulate a raised hemidiaphragm. Pleural fluid may collect in pulmonary fissures appearing as 'tumours' that can disappear on resorption of the fluid; these are known as *phantom tumours*.

The investigative procedure of choice is diagnostic pleurocentesis and analysis of the pleural fluid. Transudates are clear in colour, have a normal pH, a glucose level equal to that of serum and a white cell count of less than 1000/μl. Pleural fluid cytologic analysis may be helpful in establishing a diagnosis. The finding of over 50 per cent, lymphocytes suggests tuberculosis. A predominance of polymorphonuclear cells (50,000/ml) is seen primarily in empyemas. A predominance of eosinophils lacks diagnostic specificity but is seen in tubercular or malignant effusions (unless there is coexistent pneumothorax). A red cell count of 100,000/ml suggests a hemothorax or pulmonary infarction. Additional tests which can be performed on pleural fluid include estimation of pleural fluid adenosine deaminase (ADA), amylase and acid mucopolysaccharides. An elevated level of ADA suggests tuberculosis as a possible etiology of the effusion. Elevated pleural fluid amylase levels suggest pancreatitis, pancreatic pseudocysts or esophageal rupture. Elevated pleural fluid acid mucopolysaccharides greater than 120 mg/ml (or hyaluronic acid > 0.8 mg/ml) suggest an underlying primary pleural tumour (mesothelioma).

A milky appearance suggests a *chylothorax* or a *chyliform effusion.* A chylothorax is usually due to disruption of the thoracic duct by trauma, tumour or rarely, filariasis. Chyliform effusions are seen in rheumatoid arthritis or chronic tuberculous pleuritis. Chyliform effusions are distinguished from chylous effusions by the presence of cholesterol crystals, absence of lymphocytes, a high cholesterol but a low triglyceride level, and the absence of fat globules on staining with Sudan red. Pleural fluid acidosis (pH <7.2) is seen in empyema, tuberculosis, esophageal rupture and systemic acidosis. In empyema, this is related to an excess acid production by cellular constituents of pleural fluid such as white cells and bacteria. The low pH of effusions in rheumatoid arthritis or lupus erythematosus is

related to an exit block of H^+ ions through the inflamed pleura.

Pleural fluid cultures are obtained when an infectious etiology is suspected. Its yield in tubercular effusions is, however, low (30%). Pleural biopsy (see Chapter 11.3) increases the diagnostic yield considerably.

Management The treatment of pleural effusions depends on the correct identification of the etiologic cause. Large symptomatic pleural effusions require therapeutic thoracentesis. Upto a litre of pleural fluid may be removed at one sitting. Rapid removal of a larger amount may in rare cases, result in unilateral pulmonary edema. Indomethacin, 25 mg tid, may be used for treatment of pleural pain.

Transudative pleural effusions respond to treatment of the underlying condition. Parapneumonic effusions are treated with closed chest drainage through tube thoracostomy if they are complicated (see pathophysiology). Malignant effusions can be treated with thoracentesis. If effusions are recurrent chemical pleurodesis (obliteration of pleural space with a sclerosing agent) with tetracycline (20 mg/kg dissolved in 50 ml saline), bleomycin or talc may be attempted.

Pneumothorax

Pneumothorax refers to the presence of air in the pleural space. A pneumothorax may be an '*open*' pneumothorax, wherein there is an *open*

Table 11.22 Causes of pleural effusion

Transudates

A. Increased hydrostatic pressure
   1. congestive heart failure
   2. constrictive pericarditis
   3. superior vena cava obstruction
B. Decreased oncotic pressure
   1. nephrotic syndrome
   2. cirrhosis of liver

Hemothorax

A. Trauma
B. Malignancy
C. Endometriosis

Chylothorax

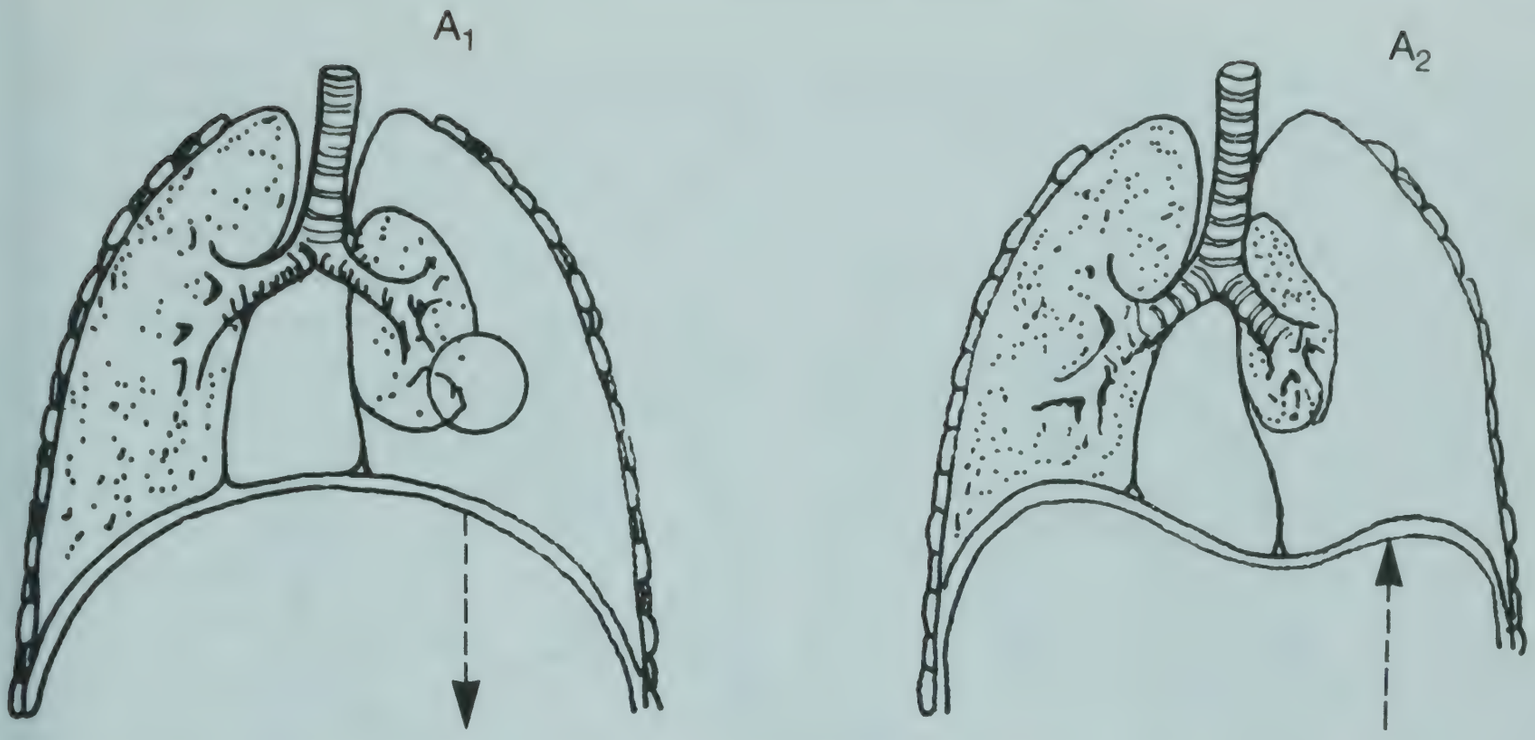
A. Trauma
B. Postoperative
C. Malignancy
D. Filariasis
E. Pulmonary lymphangiomyomatosis

Pseudochylous/chyliform

A. Rheumatoid arthritis
B. Tuberculosis

Exudates

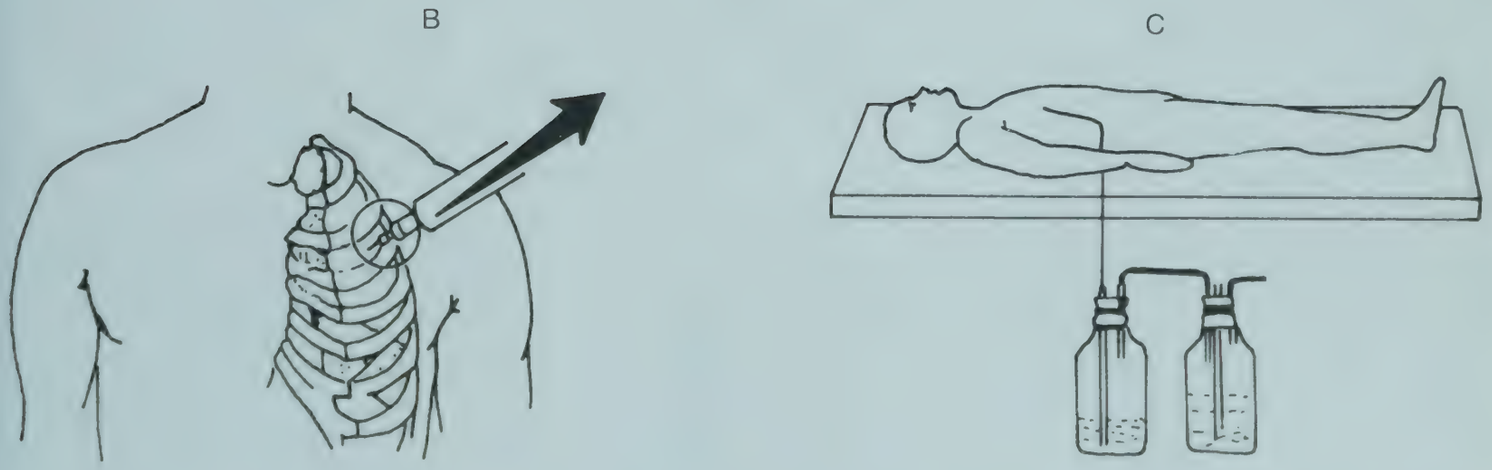
A. Infections
   1. parapneumonic
   2. tuberculosis
   3. fungi
   4. viral
   5. parasites
B. Neoplasms
   1. bronchogenic carcinoma
   2. mesothelioma
   3. metastatic carcinoma
C. Pulmonary embolism
D. Intraabdominal disease
   1. amebic liver abscess
   2. subphrenic abscess
   3. pancreatitis
   4. Meigs syndrome
E. Collagen vascular disease
   1. rheumatoid arthritis
   2. SLE
F. Miscellaneous
   1. familial mediterranean fever
   2. myxedema



Tension pneumothorax occurs when a flap-valve type of mechanism allows air into the pleural space but prevents its exit.

A_1 In this potentially lethal condition there is progressive pleural air accumulation on the side of the torn lung with each respiratory cycle

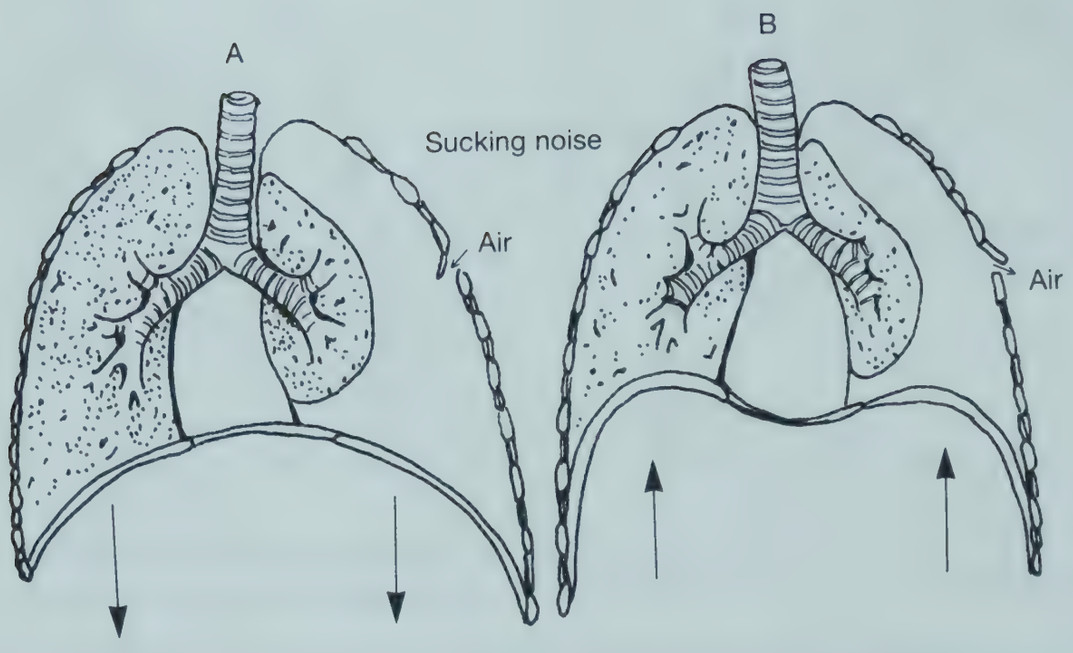
A_2 The mediastinum shifts to the opposite side, compressing the contralateral lung and interfering with ventilation and reducing venous return



B As an emergency procedure insertion of a large needle in the pleural space will provide a lifesaving vent in an upper intercostal space.

C Follow-up treatment: chest tube placement with an underwater seal

Fig 11.18 Tension pneumothorax (pathophysiology and treatment)



During inspiration (A), air moves into the pleural space, collapsing the ipsilateral lung ; with expiration (B), air moves out of the pleural space.

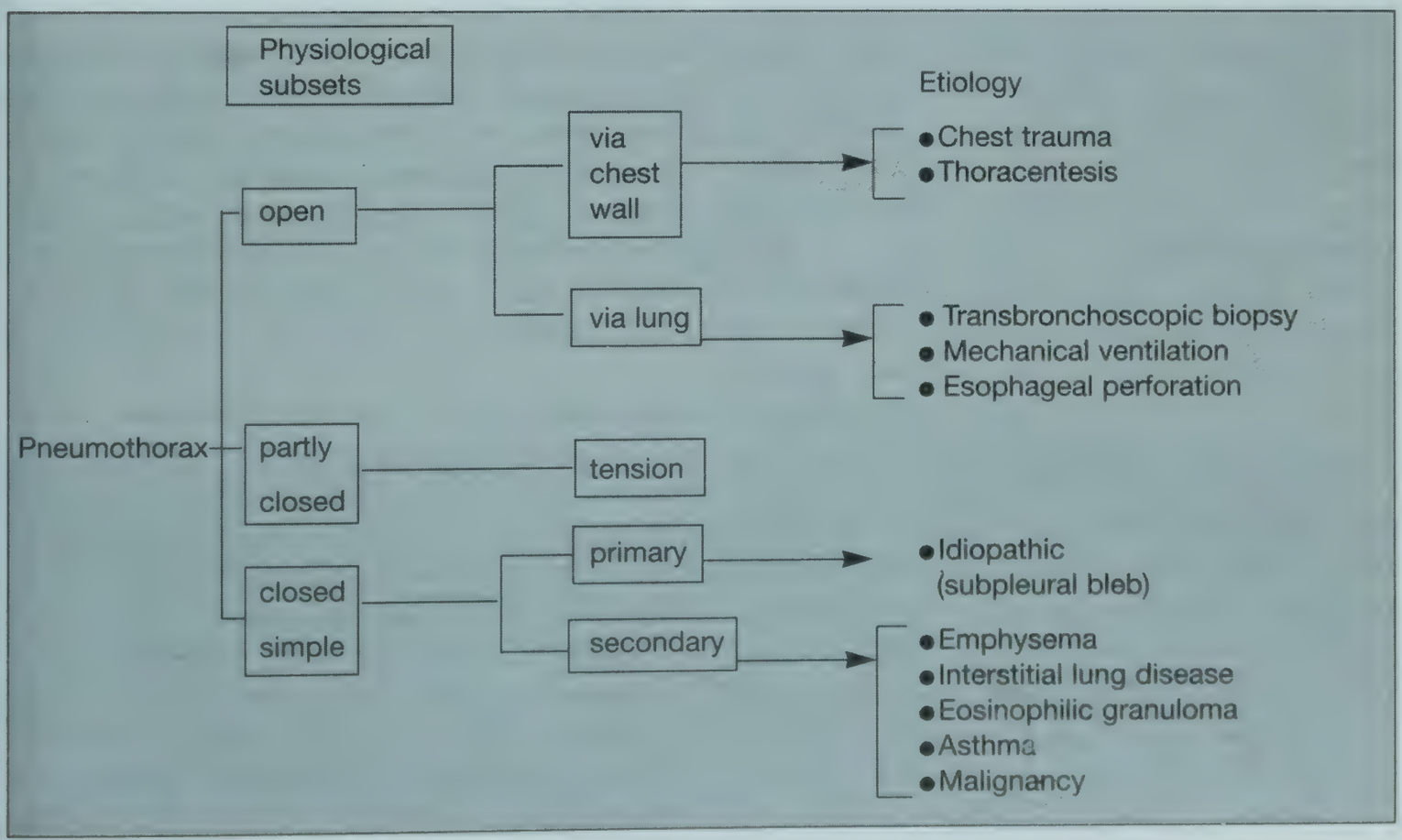
The chest wall defect must be sealed promptly with an airtight dressing, a chest tube inserted to reexpand the lung and the defect then closed surgically.

Fig 11.19 Open pneumothorax - pathophysiology and treatment

communication between the pleural space and the exterior (either via the chest wall or via the bronchial tree). It may also be '*closed*' wherein the communication through which air has entered the pleural space is closed off. A 'closed' pneumothorax may be '*simple*', when no tension exists within the pleural space. In a '*tension*' pneumothorax, the hole in the lung or the chest wall is partly closed. It allows entry of air through a check valve mechanism resulting in progressive rise in intrapleural pressure or tension. Simple pneumothoraces can be further divided into *primary* (that is, without underlying lung pathology) or *secondary* (complicating preexisting lung disease). Table 11.23 depicts the common causes of pneumothorax.

Pathophysiology (Figs 11.18, 11.19) The lung normally occupies twice the volume that it would if it were exposed to the atmosphere. The intrapleural pressure varies between 2.5 mmHg and 6.0 mmHg during quiet respiration. When air enters the pleural space, the lung on the affected side collapses as the intrapleural pressure approaches atmospheric pressure. If the hole that maintains air entry into the pleura is patent and large, resistance to movement of air into the lung may exceed the resistance to airflow into the pleura. The lung collapses further and hypoxia and respiratory distress result. If the hole into the pleura seals, air entry into the lung is maintained. Respiratory distress occurs only if there is underlying lung disease or if the pneumothorax is large. If the hole in the pleura is covered by a flap of tissue that acts as a check valve, air enters during inspiration but cannot exit during expiration. Intrapleural pressure progressively increases. The underlying lung collapses and there may be compression of the great veins and the opposite lung as well due to mediastinal shift. Hypoxemia ensues and

Table 11.23 Etiology and classification of pneumothorax



circulatory collapse may occur. A 'tension' pneumothorax can thus be fatal unless recognised and treated promptly.

Absorption of a pneumothorax Absorption of pleural air takes place through subpleural venous channels. Since the partial pressures of the gases in the pleura approximate with those of the atmosphere and their partial pressure in the venous blood is lower, a gradient-dependent diffusion ensues. The rate of diffusion and absorption also depends on the solubility of the gases. The process may take days to weeks depending on the size of the pneumothorax. With absorption of the pleural air, the lung reexpands.

Clinical features The clinical features of a pneumothorax depend on the extent of underlying collapse, the presence or absence of associated lung disease and the underlying pathophysiologic mechanism. Dyspnea of sudden onset without any wheezing and pleuritic chest pain (due to the stretching of the parietal pleura) are the commonest symptoms. In a tenth of patients, the pneumothorax may be asymptomatic being detected on a routine chest film. In subjects with underlying COPD, there may be an exacerbation of dyspnea with increased wheezing.

The clinical signs include tachypnea and cyanosis of a variable degree depending on the severity of hypoxemia. The palpatory findings include a diminished expansion of the ipsilateral side, a deviation of the trachea and the apex beat to the opposite side (reflecting a mediastinal shift) and a diminution of tactile vocal fremitus. The percussion note is hyperresonant due to an increase in the ratio of air to solid tissue. The breath sounds are faint or absent but they may have a bronchial quality if there is an associated bronchopleural fistula. Signs like the 'coin test' are seldom elicited and are of little practical importance.

Investigations The most important investigation is a chest radiograph, preferably obtained in the standing position and after maximal expiration. Radiographically, a pneumothorax appears as a clear zone with no lung markings between the chest wall and the edge of the lung; the edge of the lung is visible as a fine line running parallel to the upper and lateral margin of the chest cage. Distinction from a large emphysematous bulla can be difficult; the situation is further confounded by the fact that the two may coexist. Comparison with previous X-ray films (if available) may be helpful. Arterial blood gases reveal hypoxemia but are rarely required and probably not justified.

Treatment A small pneumothorax that has been stable over several weeks can be followed up closely with serial chest X-rays. A small 'fresh' pneumothorax (<15% lung volume) may merit hospitalisation for 48 hours for the sake of observation.

Patients who are symptomatic, and have a large pneumothorax should undergo a tube thoracostomy. The chest tube is placed with underwater seal drainage and a gentle suction applied till the lung reexpands. If there is evidence of a tension pneumothorax, a large bore needle may be applied immediately in the affected side; tube thoracostomy may be performed later.

Prognosis The risk of recurrence of a spontaneous pneumothorax is as high as 50 per cent. All subjects are advised to discontinue smoking and to avoid high altitudes, scuba diving or flying in unpressurised aircrafts. Surgical treatment may be considered for a third pneumothorax on a given side. It involves open thoracotomy with oversewing of the blebs alongwith pleural 'symphysis', that is, adhesion of the visceral and parietal pleura by scarification.

DISEASES OF THE MEDIASTINUM

The mediastinum is the extrapleural space within the thorax and between the lungs; it is bounded anteriorly by the sternum, laterally by the parietal pleura, posteriorly by the spine and inferiorly by the diaphragm. The three divisions of the mediastinum and its contents are shown in the Table 11.24.

Mediastinal Tumours

By convention, tumours of the lung and the heart are excluded from the category of 'mediastinal' tumours. Roughly half of all mediastinal tumours are malignant; 90 per cent of tumours in the middle mediastinum are malignant. Of all mediastinal tumours, roughly 55 per cent arise in the anterior mediastinum, 30 per cent in the middle mediastinum and 15 per cent in the posterior mediastinum. The commonest tumours in the the anterior, middle and posterior mediastinum are thymoma, pericardial cysts and neurofibroma, respectively.

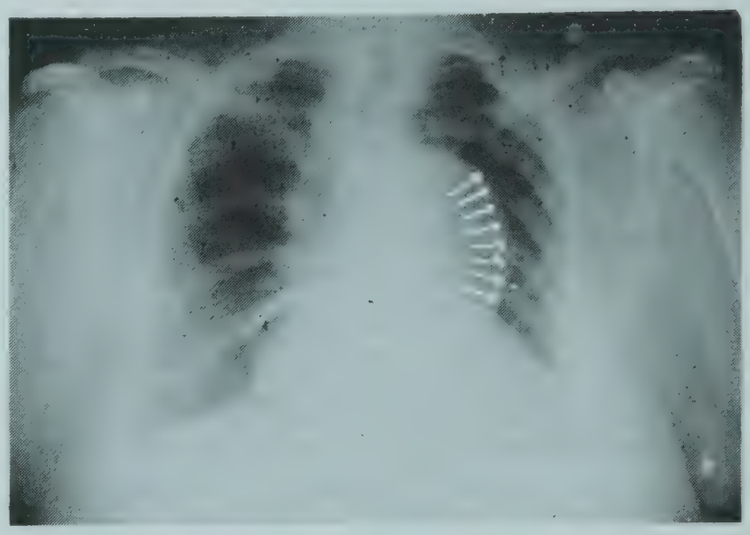


Fig 11.20 Plain X-ray of chest (PA view) of a 70-year old lady with a mediastinal mass (multiple arrows). The cardiomegaly was due to a pericardial effusion due to infiltration by the malignant fibrosarcoma. The left costophrenic angle is blunt due to a pleural effusion. This presented with progressive dyspnea, dull chest pain and dry cough.

Symptoms and signs Mediastinal tumours may be asymptomatic (being discovered accidentally on the chest X-ray) or symptomatic. Ninety-five per cent of asymptomatic masses are benign whereas 50 per cent of symptomatic masses are malignant.

The usual symptoms are related to compression of the mediastinal structures. Thus, dysphagia (esophageal compression), stridor (tracheal compression), edema of face and arms (superior vena cava compression) and Horner syndrome (compression of the cervical sympathetic chain) can result. Lymphatic compression may result in chylothorax and phrenic nerve compression may cause paralysis of a hemidiaphragm. Retrosternal pain may occur due to bone erosion. Compressive

Table 11.24 Contents of the mediastinum and common tumours

Division	*Extent*	*Contents*	*Tumours*
I Anterior mediastinum	sternum to pericardium	thymus, thyroid, prevascular lymph node	teratoma, parathyroid adenoma, lymphoma
II Middle mediastinum	pericardium to anterior spinal ligament	heart, great vessels, esophagus airways, phrenic nerve, lymph node	pericardial cyst, enteric cyst, bronchogenic cyst, neurofibroma, lymphoma
III Posterior mediastinum	anterior spinal ligament to posterior chest wall	spine, sympathetic chain, thoracic duct, lymph node	neurofibroma, lymphoma

symptoms that are more suggestive of 'invasion' by a malignant tumour include Horner syndrome and retrosternal pain.

Systemic features may be present in certain tumours: fever, weight loss in lymphomas, associated pure red cell aplasia or myasthenia in thymomas, hypertension with phaeochromocytoma and hypoglycemia with insulin secreting mesothelial tumours.

Investigations The configuration and consistency of the mediastinal tumour on the chest roentgenogram may provide a clue to its nature Fig 11.20. Thus, presence of *translucency* (indicative of fat) is seen in a lipoma, fat pad or an omental hernia. The presence of *curvilinear calcification* suggests a cyst or an aneurysm, presence of *teeth* indicates a teratoma, an *air-fluid level* indicates a bronchogenic cyst, a pericardial cyst (spring water cyst) or an esophageal perforation. A *dumbbell shape* or an hourglass configuration of the tumour or associated paraspinal widening could lead to suspicion of a neurofibroma. The preferential location of certain tumours at certain sites can yield important clues regarding the nature of the tumour. Thus, teratomas often have a pedicle beneath the aortic arch, pericardial cysts are located at the right cardiophrenic angle, bronchogenic cysts at the subcarinal space and neurofibromas lie in the paravertebral sulcus. Fluoroscopy can separate a tumour within the pulmonary parenchyma from one within the mediastinum. Computerised tomography provides information regarding the location, contents of the tumour (in the case of cysts) and invasion of other adjacent structures.

Treatment Proper treatment may require a 'tissue' diagnosis — whether obtained by thoracotomy or by CT-guided aspiration cytology.

KEY CONCEPTS

Pleural effusion

- A pleural effusion may be a *transudate* (pleural fluid protein/serum protein <0.5; fluid/serum LDH<0.6; protein<3 g/dl) or an *exudate*. Causes of a transudate (decreased oncotic or elevated hydrostatic pressure; more often left-sided) include: CHF, cirrhosis or a nephrotic syndrome. Causes of an exudate (pleural inflammation with altered permeability) include: tuberculosis (straw-coloured), neoplastic (often hemorrhagic), connective tissue disease or pancreatitis.
- Symptoms of a pleural effusion include dyspnea, and pleuritic chest pain. Physical findings include dullness on percussion, absent tactile fremitus and absent breath sounds. The chest X-ray (left lateral decubitus detects <100 ml fluid) is diagnostic; >10 mm separation of lung from chest wall indicates a large effusion with need for thoracentesis.
- Diagnostic thoracentesis with *cytologic examination* of the pleural fluid (PMN: pneumonia, abscess; lymphocytes: TB, neoplasm; malignant cells: neoplasm; blood: TB, neoplasm, infarct), *bacteriologic examination* (Gram-stain and culture) and *chemical analysis* (ADA >70u/l diagnostic of TB; TG>110 mg/dl: chylous effusion; elevated ANA in SLE; elevated rheumatoid factor and a low glucose in rheumatoid arthritis; elevated amylase in pancreatitis) is vital for determining the etiology of the effusion. Pleural biopsy is occasionally helpful.

Pneumothorax

- A pneumothorax may be *spontaneous* (simple: typically due to an apical bulla in tall young men; complicated: associated with underlying emphysema, or abscess) or *traumatic* (open: due to a penetrating chest wound; closed: when the chest wound closes). *Tension* pneumothorax occurs when air can enter but not exit the pleural spaces; it results in mediastinal shift and vascular collapse.
- If a pneumothorax is large, it can result in the acute onset of dyspnea and chest pain. Physical signs of a pneumothorax include tympany on thoracic percussion with a reduction in audible breath sounds. The chest X-ray is usually diagnostic; it reveals peripheral air

without lung markings with a central opacity representing the collapsed lung.

➢ A small pneumothorax requires no treatment. A large one requires chest tube drainage with an underwater seal. A tension pneumothorax must be immediately drained, preferably by needle aspiration; aspiration is followed by tube thoracostomy. If pneumothorax is recurrent, consider surgical or chemical *pleurodesis* (obliteration of the pleural space).

Mediastinal masses

➢ The mediastinum has three compartments which are best identified on a lateral chest X-ray: a *superior*, a *middle* (anterior) and a *posterior* compartment. Approximately 55% of all mediastinal tumours occur in the superior mediastinum, 30% occur in the middle mediastinum and the remaining 15% are found in the posterior compartment.

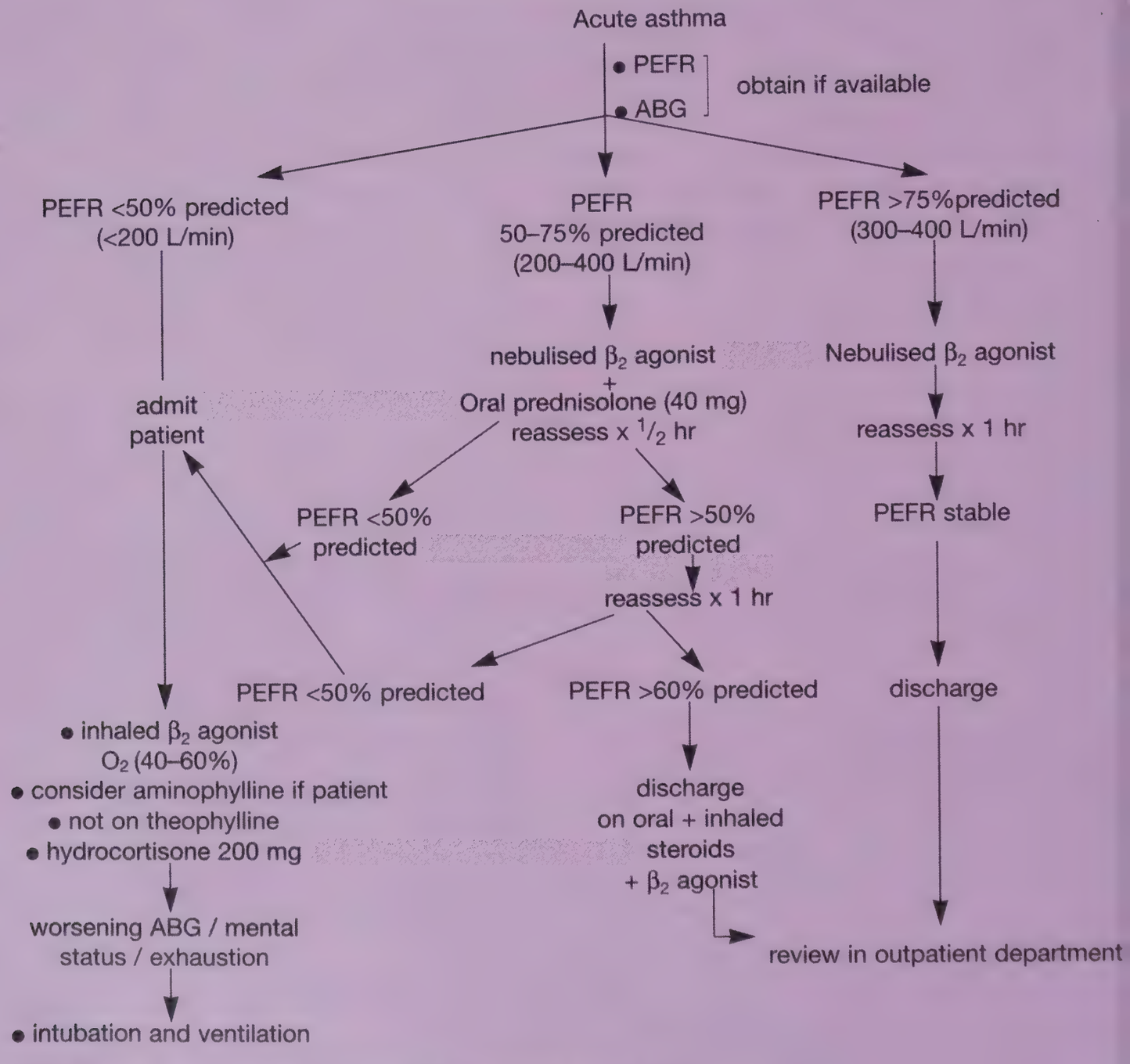
➢ The most common masses in the **anterior mediastinum** are thymomas (most common type; association with myasthenia gravis, pure red cell aplasia), lymphomas, teratomas and retrosternal goitres (associated with dysphagia and stridor).

➢ Mass lesions within the **middle mediastinum** include dermoids (calcification, teeth may be seen), pleuropericardial cysts (typically in the right cardiophrenic angle), bronchogenic cysts, lymph nodes (metastatic or granulomatous) and carcinomas. Masses in the middle mediastinum are more likely to be malignant.

➢ Neurogenic tumours are the most common masses within the **posterior mediastinum.** Neurofibromas typically lie within the paravertebral gutter. Lymphomas, myelomeningocele, esophageal diverticula and pheochromocytomas are other masses that may be found in this compartment.

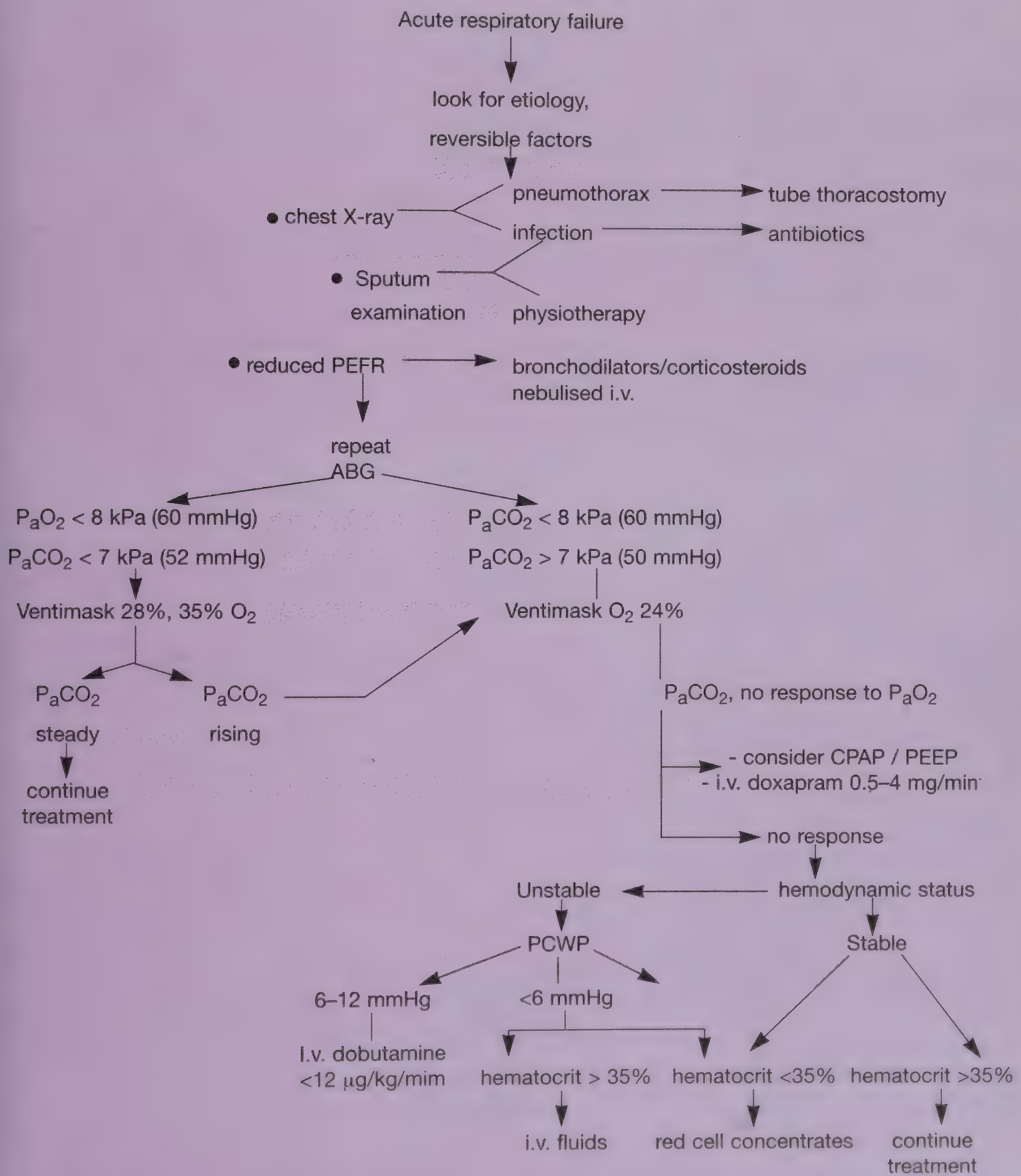
11.9 Respiratory emergencies

1. Management of acute asthma



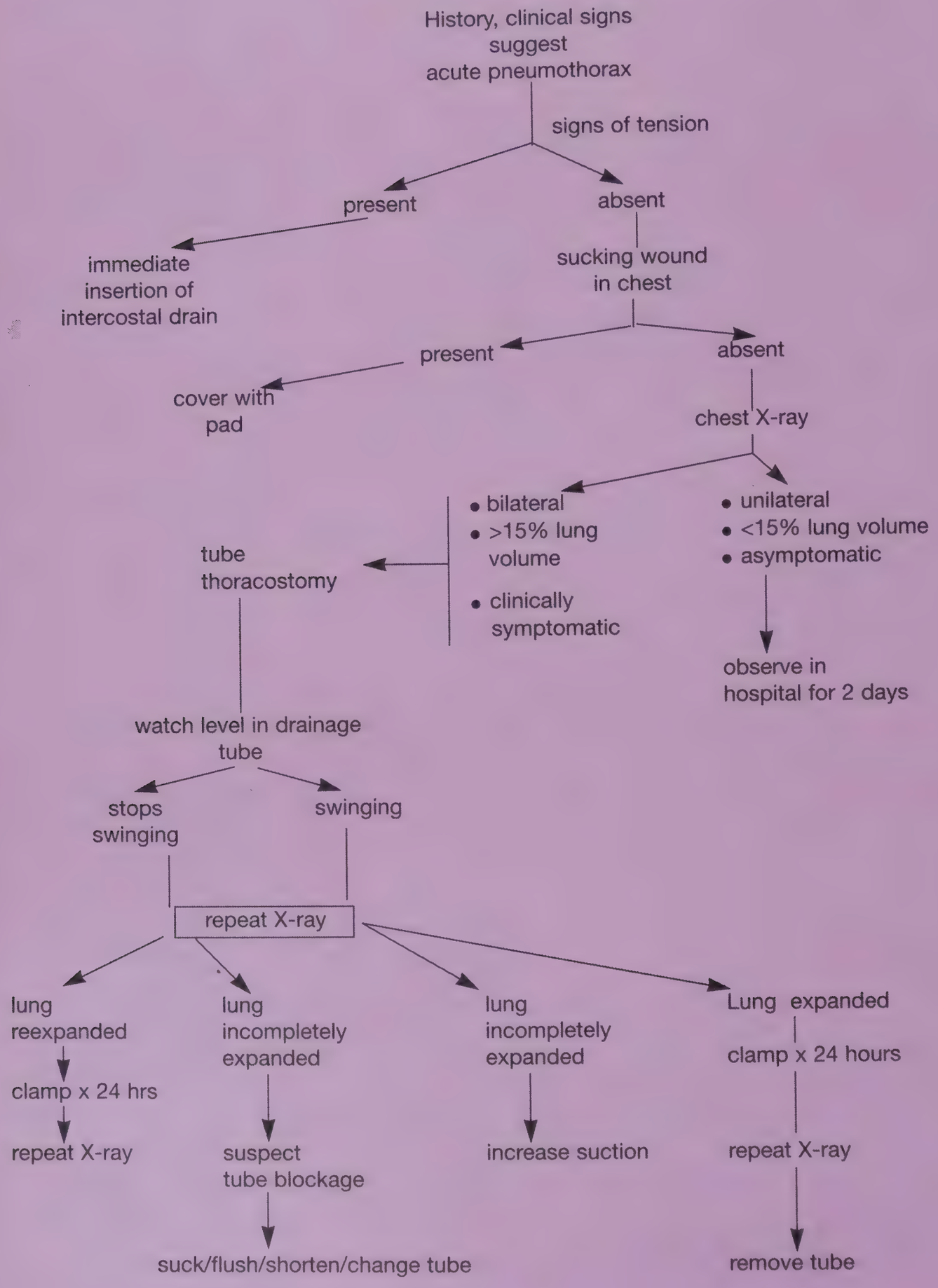
PEFR = Peak expiratory flow rate; ABG = Arterial blood gases

2. Management of acute respiratory failure



PEFR = peak expiratory flow rate; ABG = arterial blood gases;
CPAP = continuous positive airway pressure; PEEP = positive end-expiratory pressure

3. Management of acute pneumothorax



12

Disorders of the Cardiovascular System

12.1 Basic cardiovascular physiology and disturbances of cardiovascular function

STRUCTURE AND FUNCTION OF THE HEART AND BLOOD VESSELS

The cardiovascular system distributes oxygen and metabolites to all the body cells, collects carbon dioxide and waste products, and distributes hormones to distant sites. It also plays a vital role in thermoregulation. The heart is the pump which provides force for blood to circulate, and the arteries are the distribution channels which take the blood to the organs. The actual exchange of nutrients and waste products occurs in the microcirculation within the organs where the capillaries serve as the exchange vessels. The veins serve as reservoirs to collect the blood from the organs and return it to the heart.

The heart is located within the pericardial sac, which is a double layered fibrous structure. The inner layer of the pericardium is immediately adjacent to the heart. It is known as the *visceral pericardium* and forms part of the *epicardium* (outer layer) of the heart. The outer layer of the pericardium, known as the *parietal pericardium*, is separated from the inner layer by 10–20 ml of lubricating fluid called the *pericardial fluid*. The heart consists of two thin upper chambers, the right and left atria which communicate respectively with two thicker-walled lower chambers, the right and left ventricles. An interventricular septum separates the two ventricles and an interatrial septum separates the two atria. The atria communicate with the ventricles by valved openings known as the atrioventricular orifices. Each atrioventricular (AV) valve is supported by a fibrous ring called the *anulus*. The right-sided atrioventricular valve is a three-leaflet structure called the *tricuspid valve*. The left-sided atrioventricular valve is a bileaflet structure called the *mitral valve*.[1] The AV valves are attached to chords of fibrous tissue, the *chordae tendineae*, which anchor the valves to papillary muscles. These are bundles of cardiac muscle arising from the interior of the ventricular walls. The papillary muscles contract with the ventricles in systole and pull the chordae tendineae taut, thereby preventing the AV valves from leaking or prolapsing into the atria. Apart from maintaining valvular competence, the papillary muscles are also important for normal myocardial function. There are two papillary muscles in the left ventricle (anteromedial and posterolateral) and three in the right ventricle. The ventricles are separated from their respective outflow tracts by a somewhat different type of valve, the *semilunar valve*. The trileaflet *pulmonic valve* separates the right ventricle from the pulmonary artery while a trileaflet aortic valve guards the aortic opening of the left ventricle. The wall of

1 It is so called as it resembles a bishop's mitre: a high pointed hat with peaks in front and behind.

the aorta beyond the aortic valve bulges outward forming three sacs called the *sinuses of Valsalva.* From the walls of the two anterior sinuses the left and right coronary arteries emerge. The posterior sinus does not usually give rise to any coronary artery and the corresponding cusp of the aortic valve is therefore called the non-coronary cusp. The right and left coronary arteries course over the epicardial surface of the heart to distribute blood to the myocardium (Fig 12.1). The left anterior descending coronary artery (LAD) runs in the anterior inter-ventricular groove towards the apex supplying the anterior free wall of the left ventricle and the anterior two-thirds of the septum. The left circumflex artery arises from the bifurcation of the left main coronary artery (the LAD artery being the other branch) and travels posteriorly in the atrioventricular groove supplying blood to a part of the posterolateral portion of the heart. The right coronary artery runs in the right atrioventricular groove and supplies blood to most of the right ventricle and part of the interventricular septum. Most of the venous network follows the arterial system and coalesces to form the coronary sinus which drains into the right atrium. A part of the right ventricle and the atrium is drained by small anterior cardiac veins and thebesian veins which empty directly into the right atrium.

Venous blood returns from the body to the right atrium through the superior and inferior vena cavae and mixes with the cardiac venous drainage. The blood from the right atrium enters the right ventricle during diastole and is ejected by the ventricle in systole into the pulmonary artery which is positioned anterior to the aorta. The pulmonary artery bifurcates into left and right branches which carry blood to the respective lungs. The peripheral branches of the pulmonary arterial tree divide into arterioles and eventually capillaries. The pulmonary capillaries give rise to venules and the venules finally coalesce into pulmonary veins. Four major pulmonary veins join to enter the left atrium carrying the oxygenated blood from the lungs. The blood from the left atrium enters the left ventricle in diastole and is ejected in systole across the aortic valve into the aorta. The pressures and oxygen saturation of various cardiac chambers are shown in Fig 12.2.

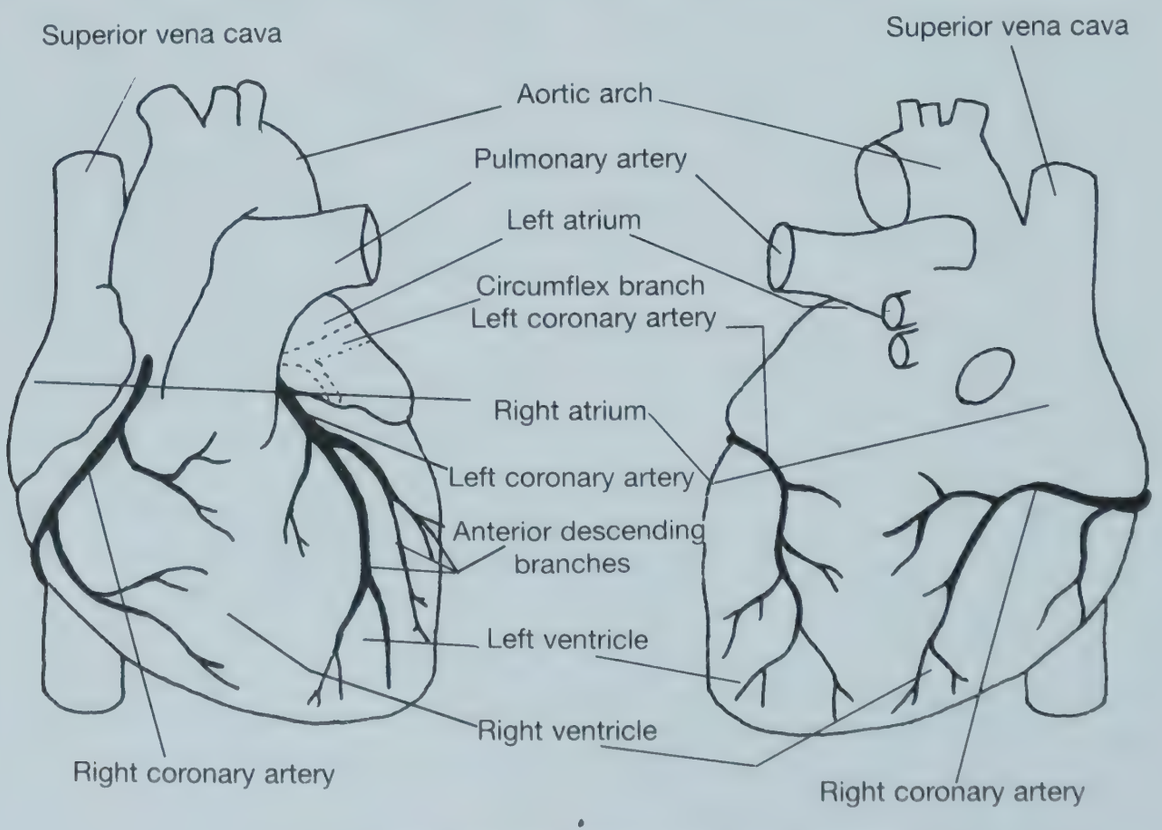


Fig 12.1 Major coronary arteries and their branches

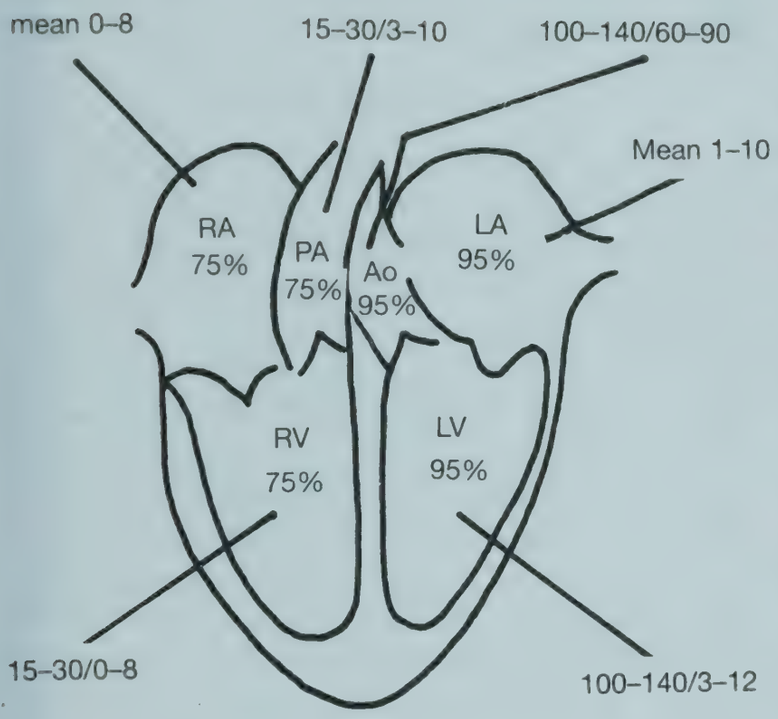


Fig 12.2 Orientation of the cardiac chambers and great vessels with normal intracardiac pressures (mmHg) and oxygen saturations (%)

PHYSIOLOGY OF CARDIAC CONTRACTION

The heart muscle (myocardium) is composed of separate cardiac muscle cells called myocytes, which are electrically connected to one another by low resistance pathways called intercalated discs. The electrical activity of one cardiac cell is transmitted to adjacent cells, the myocardium being a functional syncytium, that is, a mass of cytoplasm with numerous nuclei. The heart has two functional syncytia, the atrial and ventricular myocardium.

Each myocyte has several contractile units called *sarcomeres.* Each sarcomere has bundles of protein strands called *myofibrils.* The myofibrils are in turn composed of myofilaments of two types: the thick myofilaments are called myosin and the thin filaments are called actin. Actin filaments also contain two other proteins, troponin and tropomyosin. The myofibrils are surrounded by an extensive network of tubules known as the *sarcoplasmic reticulum.* The sarcoplasmic reticulum contains a network of tubules called cisternae which contain high concentrations of ionised calcium. The cell membrane of each myocyte is called the sarcolemma and it invaginates into the interior of the cell at the Z lines of the sarcomere where intercalated discs occur (Fig 12.3). These invaginations are called the T tubules and they conduct the electrical events at the cell membrane into the interior of the cell. Excitation – contraction coupling is the sequence of events which connect the depolarisation of the cell membrane to contraction of the muscle fibres.

The resting myocyte membrane is impermeable to sodium ions (Na^+) but very permeable to potassium ions (K^+). The intracellular K^+ concentration is much higher and the inside of the cell is electrically negative compared to the outside. This voltage difference across the cell membrane is called the resting membrane potential and varies from 60–90 mV. It is maintained by energy-requiring membrane bound ionic pumps. When stimulated, myocytes undergo what is termed 'depolarisation' or loss

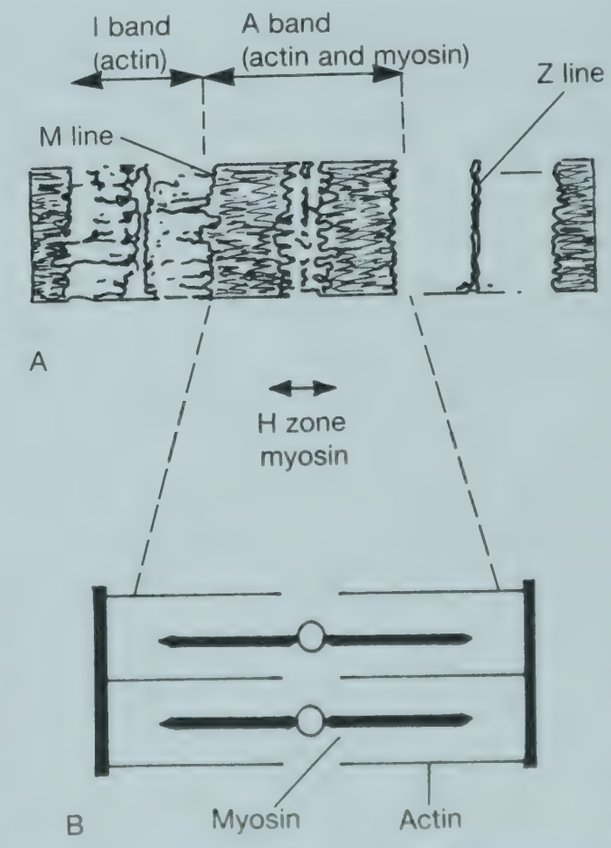


Fig 12.3 A: sarcomere as it appears under the electron microscope; B: schematic display of the location and interaction of actin and myosin

of this transmembrane potential difference. This occurs if the resting membrane potential is reduced to a critical level called the *threshold potential.* Depolarisation is spontaneous once the threshold potential is reached. This property is called the 'all or none law'. The change in membrane potential with an adequate stimulus is termed the *action potential.* The action potential can be divided into five phases (Fig 12.4). Phase 0 is mediated by the opening of membrane Na^+ channels. Phase 1 is mediated by the rapid reclosure of the Na^+ channels and opening of the calcium channels. Phase 2 is the plateau phase and coincides with continuing Ca^{++} influx and a decreased K^+ efflux. Phase 3 is the repolarisation phase with reduced calcium currents and a large increase in the outward K^+ current. Phase 4 is characterised by a steady potential in most cells other than the cells on pacemaker tissues, that is, the sinoatrial and atrioventricular nodes.

In these tissues there is a slow diastolic depolarisation (pacemaker potential) which brings the membrane potential towards the threshold potential. Since the SA node cells have the steepest slope of Phase 4, these cells constitute the normal pacemaker of the heart.

The action potential of the sarcolemmal membrane causes calcium release from the sarcoplasmic reticulum and the T tubules. The troponin component of the thin myofilaments binds the calcium ions and this causes conformational changes in the tropomyosin component encouraging crossbridge formation between actin and myosin. The result of crossbridge formation is shortening of the sarcomere length or muscular contraction. After contraction a phase of active relaxation follows wherein the intracellular calcium is again pumped back into the sarcoplasmic reticulum and the actin and myosin filaments disengage. From the above description, it is evident that the strength of contraction would depend on the number of cross bridges formed. Hence, an increase in the resting fibre length which would decrease the resting state overlap of thin and thick filaments would increase the number of available cross bridges, thereby increasing the force of contraction. This is called the Frank-Starling effect.

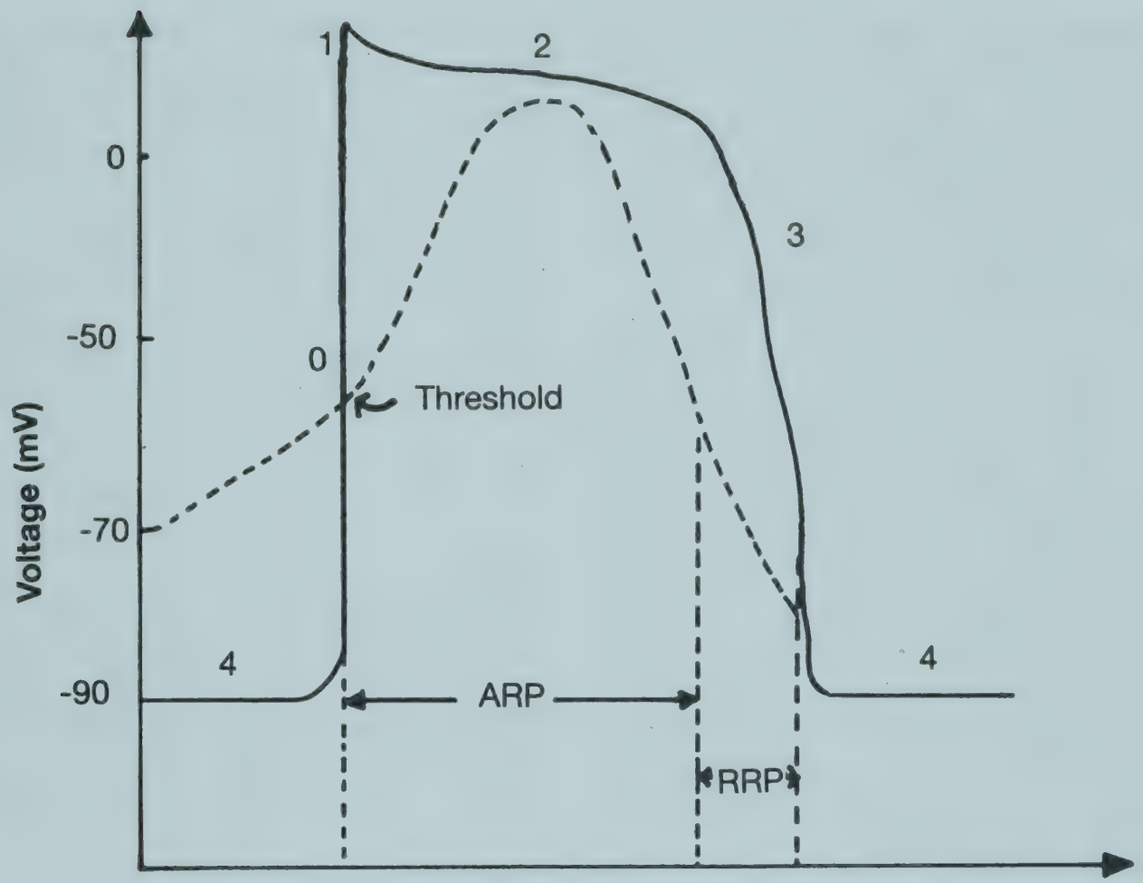
The Cardiac Cycle

The cardiac cycle includes the sequence of electromechanical events from onset of ventricular contraction (*systole*) to completion of ventricular relaxation (*diastole*). The onset of ventricular contraction coincides with the peak of the R wave of the surface electrocardiogram. During ventricular contraction intraventricular pressure increases, and when it exceeds the atrial pressure the mitral and tricuspid valves close. The closure of the atrioventricular valves results in the two components of the first heart sound (M_1 preceding T_1). During this phase (also called the *isovolumic contraction period*) the ventricles change in shape but the volume remains constant. This is followed by a further increase in the ventricular pressure which now exceeds the pulmonary and aortic pressures. The semilunar valves open and the ventricle ejects between 50–70% of its volume. Coinciding with the end of the T wave of the surface electrocardiogram, the ventricular pressure declines and falls to a level below the pressures in the pulmonary artery and the aorta. Then the aortic and pulmonary valves close. This results in the two components of the second heart sound (A_2 preceding P_2). The ventricles continue to relax and during this time ventricular volume remains constant (*isovolumic relaxation period*). When the ventricular pressure falls below that of the atria, the mitral and tricuspid valves open. This is followed by a phase of rapid ventricular filling (which coincides in timing with the third heart sound).

REGULATION OF THE CARDIOVASCULAR SYSTEM

Regulation of Blood Volume

The maintenance of normal blood volume (which is approximately 80 ml/kg body weight) represents a complex interaction of neural, endocrine and renal mechanisms. The neural



---------- slow fibres, present in SA node and AV node. Resting membrane potential is -50 to -70 mV and the conduction velocity is 2–10 cm/sec. Note the spontaneous diastolic depolarisation in phase 4 and the slow phase 0.

———— fast fibres (atrial and ventricular myocardial cells and cells in specialised conduction tissues). Resting membrane potential is -80 to -90 mV and the conduction velocity 30–100 cm/sec.

ARP: absolute refractory period, i.e., an interval in which no stimulus, however strong, can initiate an action potential

RRP: relative refractory period, i.e., an interval during which a supranormal stimulus can initiate an action potential

Fig 12.4 Action potential showing five phases

component is represented by the baroreceptors. Baroreceptors are of two types: 1) the high pressure baroreceptors which are highly branched nerve endings located in the carotid sinuses (at the bifurcation of the carotid arteries) and aortic arch; and 2) the low pressure baroreceptors (stretch receptors) which are located in the atrial wall. These receptors detect changes in central vascular volume and transmit impulses to the hypothalamus which in turn regulates pituitary function. The release of antidiuretic hormone (ADH) from the neurohypophysis[1] restores blood volume by increasing the renal reabsorption of water (at the level of the collecting ducts and distal convoluted tubule). The other stimulus for the release of ADH is mediated by osmoreceptors in the anterior pituitary. The loss of vascular volume results in hemoconcentration and increased plasma osmolality, that stimulates these osmoreceptors.

The other renal responses to a change in blood volume are mediated by the renin-

[1] Neurohypophysis = posterior pituitary.

angiotensin-aldosterone system and the atrial natriuretic peptide. A decrease in blood volume sufficient to cause a drop in renal perfusion pressure releases renin from the juxtaglomerular apparatus of the nephron. Renin reacts in plasma with a substrate called angiotensinogen to form a decapeptide called angiotensin I. Angiotensin I is converted to an octapeptide angiotensin II by the enzyme angiotensin converting enzyme (ACE) which is located primarily on the endothelial surface of the pulmonary vessels. Angiotensin II is one of the most potent vasoconstrictor substances and has a dual effect: 1) it increases peripheral vascular resistance thereby restoring blood pressure, and 2) it causes the release of aldosterone from the zona glomerulosa of the adrenals which causes renal water retention at the level of the distal tubule of the nephron (thereby reexpanding the blood volume). The atrial natriuretic peptide (ANP) is found in storage granules in some cells of the atria. The peptide as its name suggests, enhances renal excretion of sodium and water by dilating renal afferent arterioles (thereby increasing the glomerular filtration rate). Hypovolemia causes a lesser distension of atrial walls and therefore, a lesser release of the ANP and thereby promotes renal water retention and plasma reexpansion.

Regulation of Arterial Pressure

The arterial pressure is regulated within a narrow range by the complex interaction of the baroreceptors, the central nervous system and the autonomic nervous system. The high pressure baroreceptors are sensitive to stretching of the arterial walls which also depends on the arterial pressure. An increase in arterial pressure elicits a reflex response whereby afferent neural activity over the sinus and aortic bodies result in a vagally mediated slowing of the heart and a reduction in arterial pressure due to peripheral arteriolar vasodilatation. The central nervous system has areas located within the reticular formation of the brainstem that regulate systemic arterial pressure. A cardioaccelerator centre elicits a 'pressor' response when stimulated and a cardioinhibitory centre elicits a 'vasodepressor' response. Cortical influences integrate these brainstem responses. The autonomic nervous system also has profound influences on arterial pressure. Sympathetic preganglionic fibres arise from the cell bodies in the intermediolateral grey horns of the thoracodorsal spinal cord, exit through the ventral root and proceed to the paravertebral chain of sympathetic ganglia where they synapse with the postganglionic fibres. The sympathetic preganglionic fibres are all cholinergic whereas sympathetic postganglionic fibres may be adrenergic or cholinergic. The adrenergic fibres have a pressor effect by causing vasoconstriction in most vascular beds. The cholinergic fibres innervate some exocrine glands and the skeletal muscles where they cause vasodilatation. The sympathetic adrenergic receptors may be α receptors or β receptors. α receptors are stimulated by epinephrine and norepinephrine and cause vasoconstriction.[1] These receptors are of two types: 1) α_1 receptors are postsynaptic and stimulatory (pressor); 2) α_2 receptors may be presynaptic or postsynaptic. α_2 receptors when stimulated cause a vasodepressor effect by inhibiting the release of neurotransmitters at the synapse thereby reducing the sympathetic tone. β receptors are most strongly stimulated by isoproterenol and least stimulated by norepinephrine. These receptors are of three types: 1) β_1 receptors are found predominantly in the myocardium and activation of these receptors results in an increase in contractility (known as a positive inotropic response), and an increase in the heart rate (known as a positive chronotropic response). 2) β_2 receptors are found at other sites, most importantly, on bronchial musculature and vascular smooth muscle where they mediate bronchodilatation and vasodilatation on stimulation. 3) β_3 receptors mediate catecholamine-stimulated thermogenesis (in brown fat) and lipolysis (in white fat) and play a role in the pathogenesis of

[1] Except presynaptic α_2 receptors that cause vasodilatation

obesity. The effect of various drugs on these receptors is shown in Table 12.1.

The parasympathetic nervous system arises from the cranial and sacral outflows of the central nervous system. Parasympathetic stimulation has no effect on the vascular tone or on cardiac contractility as most blood vessels and ventricles have no parasympathetic innervation. The major effect is a vagally-mediated decrease in heart rate known as negative chronotropic effect due to the effects on the sinoatrial and atrioventricular nodes.

Examination of the Pulse

Examination of the cardiovascular system includes a careful palpation of the peripheral arterial pulses—the carotid, brachial, radial, femoral, popliteal, posterior tibial and dorsalis pedis. Arterial pulses are examined for the rate, amplitude, volume, time to peak (rate of onset and decline) and symmetry. Unequal upper or lower limb pulses may suggest peripheral arterial atherosclerotic disease in the elderly and Takayasu's disease in the young. In supravalvular aortic stenosis, the arterial jet is directed towards the right innominate producing stronger carotid and brachial pulses on that side. Strong pulses in the upper extremities with weak or absent pulses in the lower extremities is suggestive of coarctation of the aorta.

Abnormalities of the pulse in various disorders are depicted in Fig 12.5. Being closest to the aorta, the carotid pulses provide the best information about cardiac function. Besides palpation, the physician should also perform auscultation over these pulses as a 'bruit' over a vessel is often the initial indication of a luminal narrowing of the vessel (Fig 12.6).

Examination of Blood Pressure

Blood pressure is usually measured in the patient's arm, with the subject seated and the arm slightly flexed and supported on a table or a pillow. The deflated bladder of the measuring cuff is centered over the brachial artery, just medial to the biceps tendon with the lower edge 2 to 3 cm above the antecubital fossa. Proper cuff size is critical. The cuff should be approximately two-thirds the width of the arm, or 15 cm in an average adult. A short cuff falsely elevates the blood pressure reading. The systolic pressure is initially checked by the palpatory method to avoid misleading by any 'auscultatory gap' during the auscultatory method (Fig 12.7a). The cuff is inflated while palpating the brachial artery till the pulse is no longer felt. After ascertaining the reading by the palpatory method, the bell of the stethoscope is placed over the brachial artery (Fig 12.7b) and the cuff is inflated to a pressure of 20–30 mmHg above the palpable systolic pressure. The use of the bell of the stethoscope is recommended as it is more effective than the diaphragm in transmitting the low-pitched sounds produced by the turbulent

Table 12.1 Drugs affecting the sympathetic nervous system

	α receptors			*β receptors*		
Effect	*Non-selective* ($\alpha_1 + \alpha_2$)	α_1	α_2	*Non-selective* ($\beta_1 + \beta_2$)	β_1	β_2
Antagonists	Phenoxybenzamine Phentolamine Tolazoline	Prazosin Labetalol	Yohimbine	Propranolol Timolol Sotalol Nadolol Labetalol	Acebutalol* Atenolol* Metoprolol* Betaxolol	
Agonists	Epinephrine Methoxamine Metaraminol		Clonidine	Isoproterenol	Dobutamine	Terbutaline Metaproterenol

* At high doses these drugs can be non-selective β-blockers.

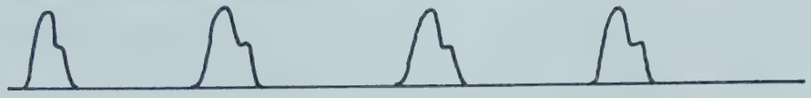
POSSIBLE CAUSE

Small, weak pulse

Hypovolemia
Physical obstruction to left ventricular output, e.g., aortic stenosis

A weak pulse may be difficult to feel, and the vessel may be obliterated easily by the fingers. The pulse may 'fade out' (be impalpable). The pulsation is slower to rise, has a sustained summit, and falls more slowly than the normal. A pulse which is weak and variable in amplitude is called thready.

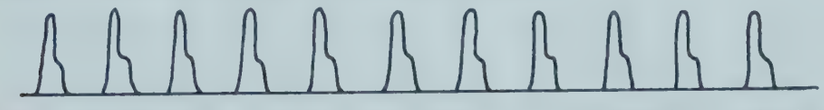
Large, bounding pulse



Exercise
Anxiety
Fever
Hyperthyroidism

The large, bounding pulse (also called hyperkinetic or strong pulse) is readily palpable. It does not 'fade out' and is not easily obliterated by the examining fingers.

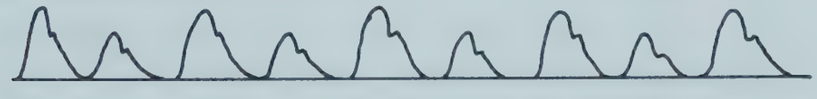
Water-hammer pulse (Corrigan pulse)



Patent ductus arteriosus
Aortic regurgitation

The water-hammer pulse (also known as collapsing pulse) has a greater amplitude than the normal pulse, a rapid rise to a narrow summit and a sudden descent.

Pulsus alternans



Left ventricular failure

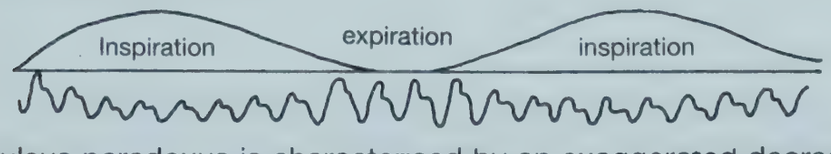
Pulsus alternans is characterised by alternation of a pulsation of small amplitude with the pulsation of large amplitude while the rhythm is normal.

Bigeminal pulse

Disorder of rhythm

Bigeminal pulsations result from a normal pulsation followed by a premature contraction. The amplitude of the pulsation of the premature contraction is less than that of the normal pulsation.

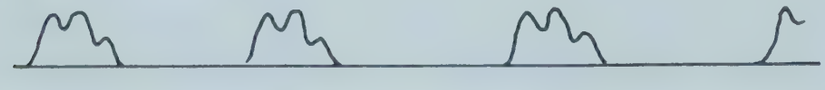
Pulsus paradoxus



Tracheobronchial obstructon
Bronchial asthma
Emphysema
Pericardial effusion
Constrictive pericarditis

Pulsus paradoxus is characterised by an exaggerated decrease (>10 mmHg) in the amplitude of pulsation during inspiration and increased amplitude during expiration.

Pulsus bisferiens



Aortic stenosis combined with aortic insufficiency

Pulsus bisferiens is best detected by palpation of the carotid artery. This pulsation is characterised by two systolic peaks. The first is termed percussion wave and the second is called the tidal wave. Although the mechanism is unclear, the first peak is believed to be due to the pulse pressure and the second, reverberation from the periphery.

Fig 12.5 Abnormalities of the pulse

a b

Fig 12.6 Auscultation for bruits a: Carotid artery; b: Temporal artery

flow in the artery (the Korotkoff sounds). The cuff is then deflated at a rate of 2 to 3 mmHg per second listening for phase 1 (systolic pressure) and phase 5 (diastolic pressure) of the Korotkoff sounds (Fig 12.8). When the sounds are heard till zero (as in aortic regurgitation), the phase 4, that is muffling of sounds, is taken as the diastolic pressure. Important factors in the measurement and interpretation of blood pressure are listed below.

To measure the blood pressure in the legs, the patient is asked to lie prone. The thigh cuff bladder is centered over the posterior thigh on the distal third of the femur and the popliteal artery is used for auscultation. Blood pressure taken at the leg is usually 10 mmHg higher than at the arm.

Guidelines for measuring blood pressure

1. In general, it is better to use a bigger cuff than a smaller cuff, provided it fits

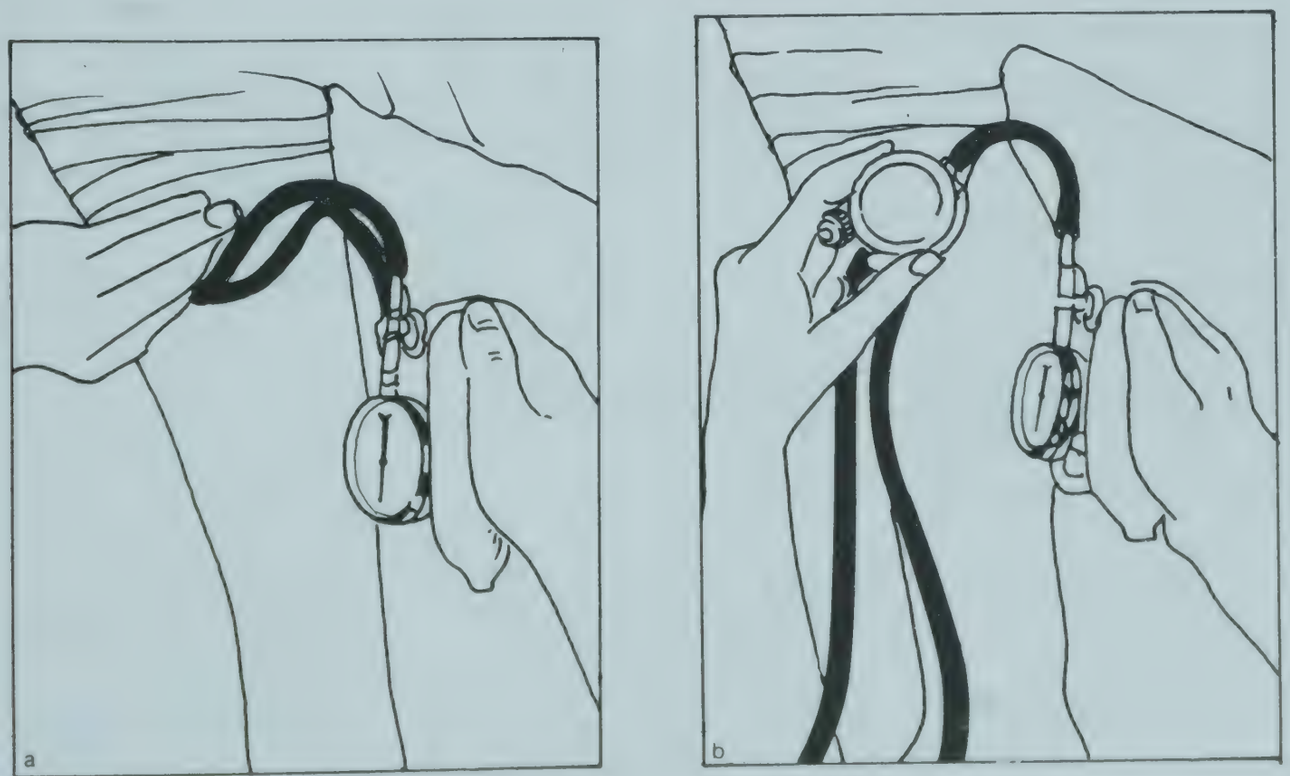


Fig 12.7 a, b Blood pressure measurements

comfortably on the arm. The size of the cuff is measured by the width of the bladder and not by the width of the cloth.

2. The diagnosis of hypertension is to be made over time. A few readings on any given day may not be diagnostic. This does not hold true when the patient has malignant hypertension requiring immediate care.
3. The mercury column sphygmomanometer is perhaps the most reliable of the available devices for measuring blood pressure. The aneroid sphygmomanometer tends to lose its accuracy with age and use.
4. Pressures taken when the patient is supine tend to be higher than those taken when the patient is sitting. When documenting a patient's blood pressure measurements over time, the same position must be used. The standards we use have been set for patients in the seated position.
5. Blood pressure generally increases with age in children.
6. A child who is taller and heavier will have a higher blood pressure reading than another person of the same age, of average height and weight.

Examination of the Neck Veins

In order to examine the neck veins, the patient is asked to lie down and his upper trunk is elevated and rested comfortably on a pillow (Fig 12.9), usually at an angle of 45 degrees. The external jugular vein is inspected for distension and the internal jugular veins are inspected for pulsation. Normally the external jugular vein should not be seen above the clavicles with the trunk reclining at an angle of 45 degrees.

The vertical height of the internal jugular vein from the angle of Louis plus 5 cm approximates the central venous pressure (normal 5–9 cm of H_2O). The normal jugular venous pressure (JVP) falls with inspiration (augmented right atrial filling) and increases with expiration. If the opposite occurs, that is, JVP increases in inspiration and decreases with expiration (also called Kussmaul's sign) constrictive pericarditis or a restrictive cardiomyopathy may be suspected. The jugular venous wave form is timed with reference to the first and second heart sounds; this is accomplished by listening to the heart while examining the neck veins.

The normal wave form comprises of three positive waves (a,c,v) and two negative waves (x and y descents). The a wave occurs before the first heart sound, (S_1) and is due to atrial contraction. The c wave occurs with S_1 and is due to the upward bulging of a closed tricuspid valve during right ventricular systole. The c wave is followed by the x descent which is due to atrial relaxation. The v wave is produced along with

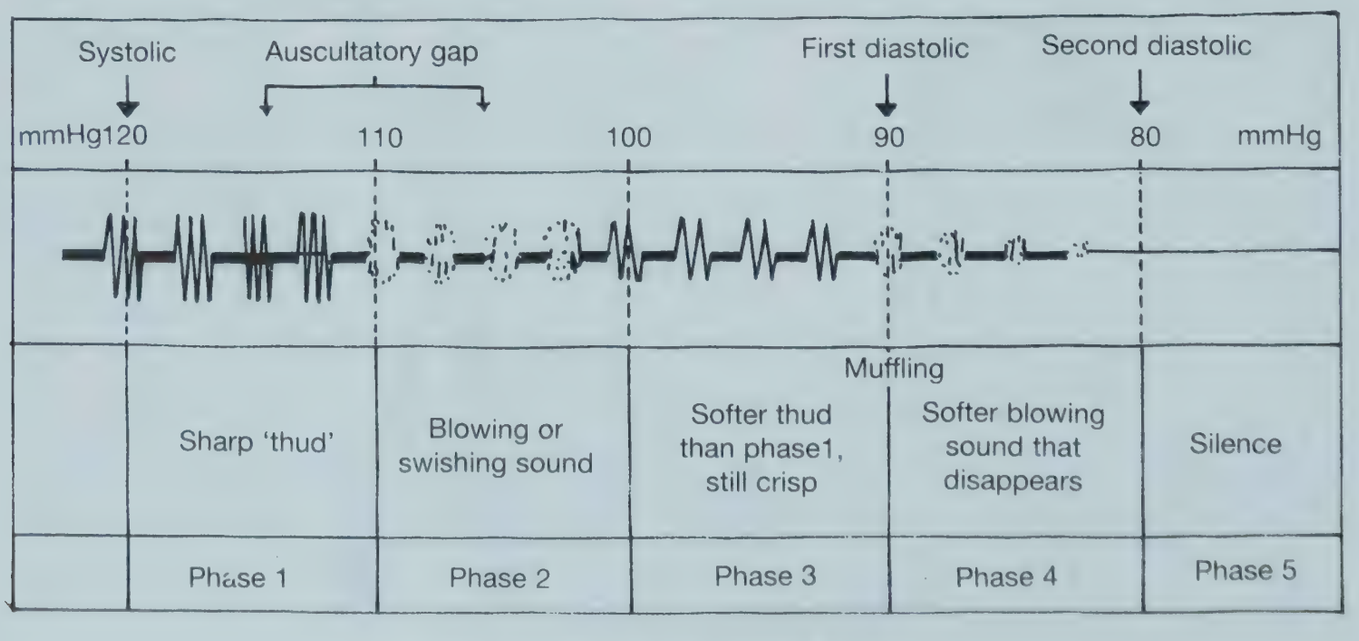


Fig 12.8 Phases of Korotkoff sounds

the second heart sound (S_2) and is due to blood returning from the periphery to the right atrium during systole when the tricuspid valve is closed. The y descent is a diastolic event occurring after S_2 when the tricuspid valve opens and the right atrium empties.

Abnormalities of the venous wave form are shown in Fig 12.10.

CARDIAC AUSCULTATION

Auscultation (Fig 12.11) is performed with a high quality stethoscope with both a bell and a diaphragm. The diaphragm is used to auscultate higher pitched sounds such as S_1, S_2, ejection clicks and high pitched murmurs such as that of aortic stenosis. The bell is used to hear low frequency sounds such as S_3, S_4 and low pitched murmurs such as that of mitral stenosis. The four main anatomic chest areas used for auscultation are the cardiac apex (termed the mitral area as sounds and murmurs originating from the mitral valve are best heard here), the lower left sternal border (termed the tricuspid area as sounds and murmurs originating from the tricuspid valve are best heard here), the second left interspace (termed the pulmonic area as sounds and murmurs originating from the pulmonic valve are best heard here) and the second right intercostal space (termed the aortic area for similar reasons as above).

The first heart sound (S_1)

The first heart sound is produced by the closure of the mitral (M_1) and tricuspid (T_1) valves in that order. S_1 is loudest at the apex and occurs just before the peak impulse of the carotid pulsation (a convenient reference point for timing for beginners). The two components of the first sound are usually merged but can occasionally be heard as split sounds; identification of the splitting of S_1 is not as valuable as identification of the splitting of the second heart sound.

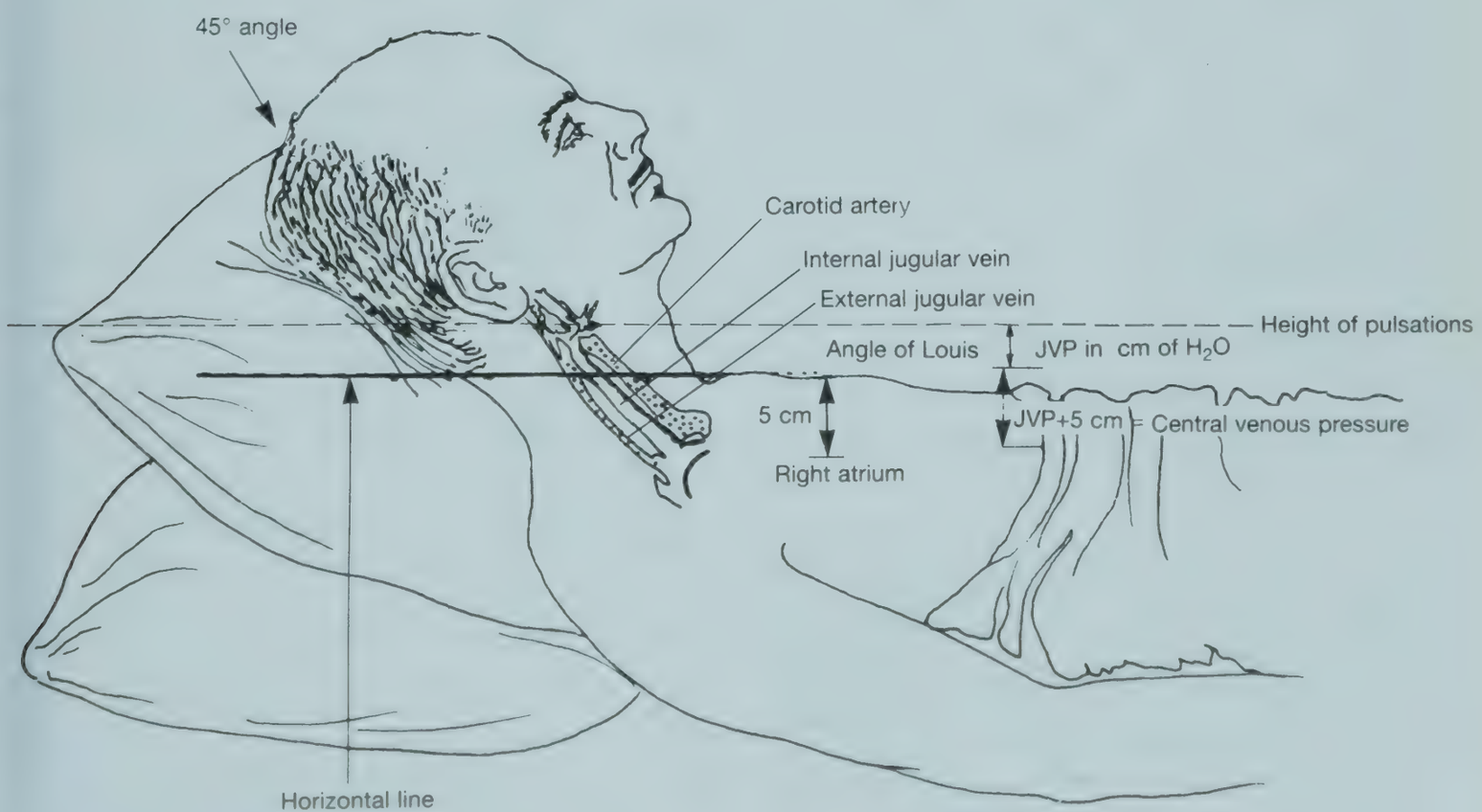


Fig 12.9 Inspection of jugular venous pressure

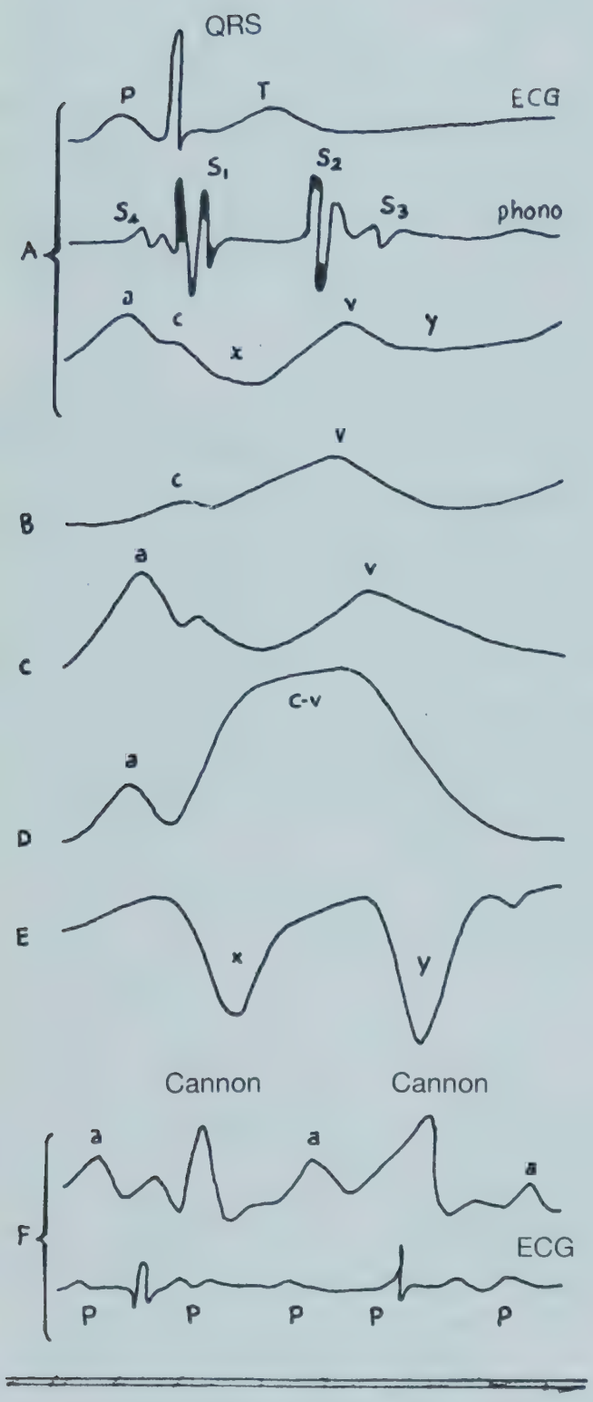


Fig 12.10. Normal and abnormal jugular venous pulse tracings. A: Normal jugular pulse tracing with simultaneous electrocardiogram and phonocardiogram. B: Loss of 'a' waves in atrial fibrillation. C: Large 'a' waves in tricuspid stenosis. D: Large 'c-v' waves in tricuspid regurgitation. E: Steep 'x' and 'y' descents in constrictive pericarditis. F: Jugular venous pulse tracing and simultaneous electrocardiogram during complete heart block, demonstrating cannon 'a' waves occurring when the atrium contracts against a closed tricuspid valve during ventricular systole.

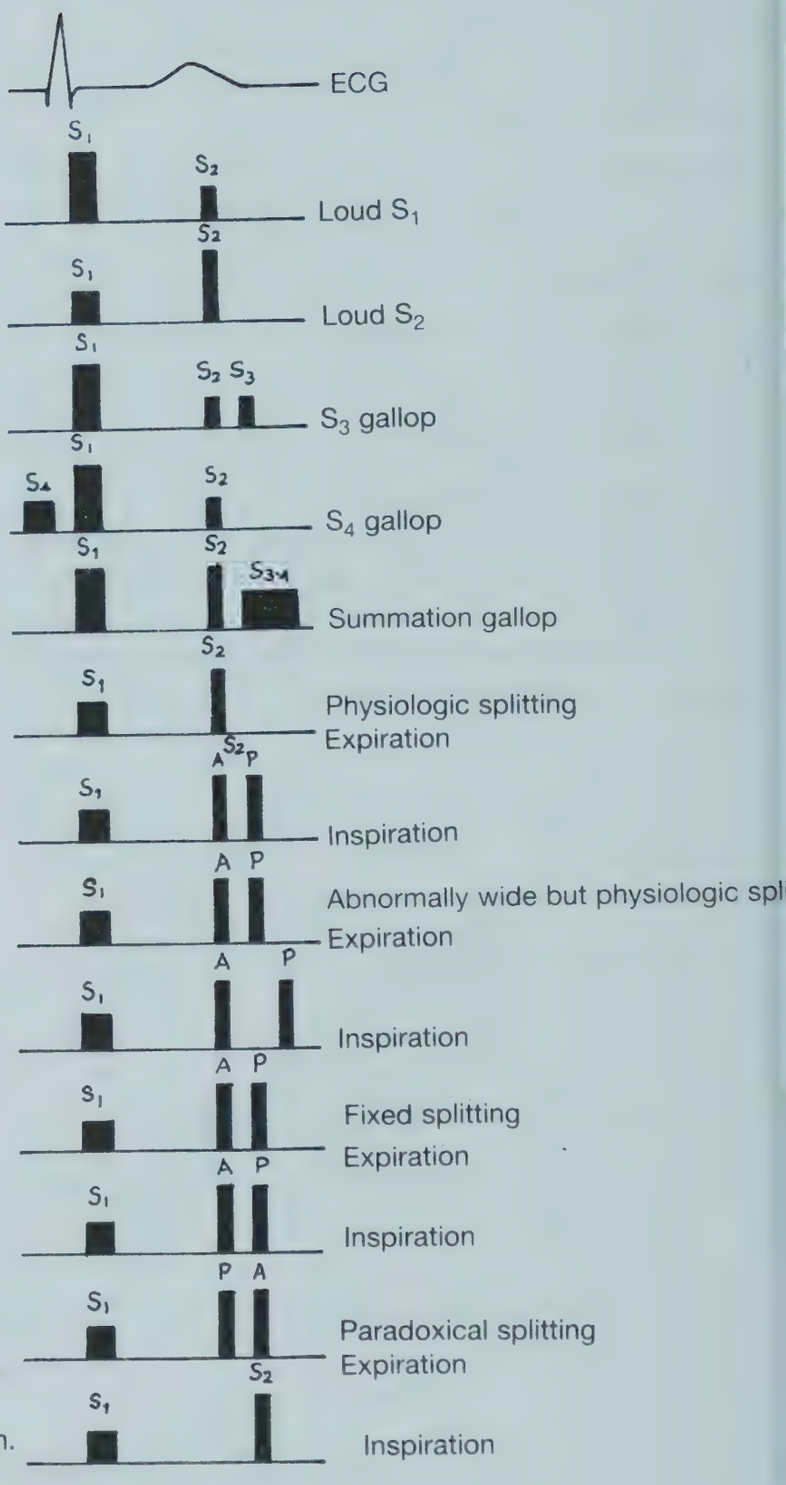


Fig 12.11 Abnormal heart sounds can be related to abnormal intensity, the abnormal presence of a gallop rhythm or the abnormal splitting of S_2 with respiration.

Since the first heart sound is due to the movement of the mitral and tricuspid leaflets, its intensity depends on three factors (other than thickness of the chest wall and the amount of intervening lung parenchyma[1]) : 1) the position of the mitral and tricuspid valves at the onset of ventricular contraction. When there is a short PR interval (tachycardia or preexcitation), the mitral valve is more widely open at the onset of ventricular systole. This causes the sudden abrupt excursion of the mitral valve to close itself, with a consequent increase in the intensity of S_1. An increased pressure gradient between the left atrium and the left ventricle (such as that seen in mitral stenosis) also causes the mitral valve to be more open at the onset of ventricular systole with a resultant loud S_1. 2) the status of the mitral and tricuspid valve leaflets. When the mitral valve leaflets are destroyed (flail valve) or the mitral annulus dilated (severe mitral regurgitation) the mitral valve leaflets cannot coapt during ventricular systole. The S_1 is therefore, soft. Though mitral stenosis is classically associated with a loud S_1, when the mitral valve is calcified and therefore immobile S_1 is soft. 3) the force of ventricular contraction. When the force of left ventricular contraction is increased (thyrotoxicosis, fever, exercise, anemia), the mitral valve is shut close with force and S_1 is loud. When the force of left ventricular contraction is diminished (as with congestive heart failure or cardiogenic shock), the first heart sound may be faint.

The second heart sound (S_2)

The second heart sound is produced by the closure of the aortic and pulmonary valves in that order, the aortic component A_2 being louder than the pulmonic component P_2. The interval between A_2 and P_2 varies with the phase of respiration. The increased venous return to the right side of the heart which occurs during normal inspiration prolongs right ventricular ejection so that P_2 is delayed as compared to A_2. This produces inspiratory splitting and the expiratory merging of A_2 and P_2. This splitting of S_2 is best appreciated over the pulmonic area. The aortic valve closure sound is increased in systemic hypertension and diminished in aortic stenosis. The pulmonary valve closure sound is increased in pulmonary hypertension and diminished in pulmonic stenosis. The inspiratory splitting of S_2 (which is normally 40 to 50 ms) can be exaggerated. This exaggeration is termed *wide variable splitting* and can occur whenever P_2 is delayed (delayed right ventricular activation due to right bundle branch block, prolonged right ventricular ejection as in pulmonary embolism, or obstruction of right ventricular outflow tract) or whenever A_2 is relatively early (shortened left ventricular systole as in mitral regurgitation or ventricular septal defect). The S_2 may be widely split in both inspiration and expiration (wide fixed split) whenever there is an abnormally large quantity of blood entering the right ventricle during both phases of respiration, and the increase in right ventricular blood volume during inspiration is comparatively negligible. This happens in an atrial septal defect or in severe right ventricular failure. Reversed splitting (or paradoxic splitting) of the second sound is present when splitting of A_2 and P_2 occurs during expiration but the components merge during inspiration. This occurs whenever A_2 is delayed as in prolonged left ventricular systole (in the case of left bundle branch block, left ventricular outflow tract obstruction or severe left ventricular failure, decreased impedance of the systemic vascular bed (as in aortic regurgitation or patent ductus arteriosus). The second sound may appear single when either component is absent: absent A_2 in severe aortic stenosis, absent P_2 in severe pulmonic stenosis or tetralogy of Fallot, or when the two components appear fused (Eisenmenger's ventricular septal defect[2]).

[1] The intervening interface between the stethoscope and heart includes the pericardial space, the lungs and the chest wall. Therefore a large pericardial effusion, hyperinflated lungs (emphysema) and a thick chest wall (obesity) can decrease the intensity of all heart sounds and murmurs.

[2] Refers to ventricular septal defect with severe pulmonary hypertension which is irreversible

Third and fourth heart sounds (S_3 and S_4)

The third and fourth heart sounds are low pitched diastolic sounds which are termed *gallops*. During periods of tachycardia, the diastolic period is so shortened that the two sounds appear merged together as a 'summation gallop'.

The third heart sound, also called a protodiastolic gallop occurs during early diastole (0.20 seconds after A_2) due to the rapid flow of blood from the atria into the ventricles. It is due to mitral and tricuspid valvular and left and right ventricular myocardial movement. A left ventricular S_3 is heard with the bell of a stethoscope over the apex and signifies the presence of left ventricular dysfunction in middle-aged subjects. A benign left ventricular gallop may normally be heard in children, young adults, pregnant women, and in patients with anemia, thyrotoxicosis, ventricular septal defect or mitral regurgitation. The S_3 in these patients is related to accelerated blood flow into the left ventricle rather than ventricular dysfunction. A right ventricular S_3 is heard over the left lower sternal edge and increases on inspiration. It may reflect right ventricular dysfunction or may be physiologic (as in severe tricuspid regurgitation).

The fourth heart sound, also called a presystolic or atrial gallop, occurs in late diastole coincident with atrial contraction before the first heart sound. The origin of the sound is a combination of valve and ventricular myocardial movement. S_4 gallops signify stiff ventricles that have a reduced compliance and which are, therefore, more dependent on forceful atrial contraction (the atrial kick) for adequate filling during diastole. The stiffness of the ventricle may be age-related (a physiologic soft S_4 in the elderly), due to ischemic heart disease or due to ventricular hypertrophy (hypertension, aortic stenosis or hypertrophic cardiomyopathy). Since the S_4 is due to atrial systole, it is absent in arrhythmias such as atrial flutter or fibrillation.

Ejection sounds (click)

An ejection sound is an extra systolic sound heard just after the first heart sound and is heard best with the diaphragm of the stethoscope. An aortic ejection sound is heard best in the aortic area and is due to systolic 'buckling' of the abnormal aortic valve leaflets as in a congenital bicuspid aortic valve. It does not vary with respiration (constant click). A pulmonary ejection sound is due to the systolic buckling of abnormal pulmonary valve leaflets as in pulmonic stenosis. This ejection sound is unique among right heart auscultatory findings in that with inspiration it decreases in intensity (and is hence called the inconstant click). Ejection sounds also occur whenever either ventricle ejects rapidly into a dilated aorta, as in aortic regurgitation, or a dilated pulmonary artery, as in an atrial septal defect.

Midsystolic click

A midsystolic click is heard at the apex with the diaphragm of a stethoscope in mitral valve prolapse syndrome, presumably related to chordal 'snaps' as the chordae tendineae try to check the buckling movement of the prolapsing leaflets.

Other sounds

The opening snap (OS) of the mitral valve is a diastolic sound occurring 0.04 to 0.12 seconds after the second sound in mitral stenosis when a mobile mitral valve buckles from the inward rush of blood from the left atrium into the left ventricle. The more severe the mitral stenosis, the higher the left atrial pressure and the earlier the rush of blood into the left ventricle; the A_2-OS interval therefore shortens with severe mitral stenosis.

A left atrial myxoma can produce a diastolic sound similar in timing to an opening snap and presumably related to the movement of the tumour on its stalk into the mitral orifice in diastole (tumour plop).

A pericardial knock is a diastolic sound occurring 0.12 to 0.20 seconds after A_2 in constrictive pericarditis. It is due to the rapid rush of blood into a left ventricle restricted by a fibrosed pericardium.

Murmurs

Normal vascular flow is laminar or streamlined and, therefore, silent. Murmurs are caused by turbulent blood flow resulting from the narrowing of a valve or a change in the direction of blood flow. A turbulent flow sets up vibrations in tissues that can be heard as murmurs. Murmurs are characterised by their location, timing, shape, intensity, radiation, quality and response to maneuvers. Murmurs that are caused by the flow of blood from a high pressure chamber to a low pressure chamber during systole typically occur throughout the systole since a pressure gradient is present throughout, and are called pansystolic or holosystolic. The murmurs associated with mitral or tricuspid regurgitation and ventricular septal defects are holosystolic. The murmurs of valvular stenoses (aortic or pulmonic) are systolic, begin with S_1 and end before S_2 and are crescendo-decrescendo in shape. They are also called *ejection systolic murmurs*. Stenoses of atrioventricular valves typically produce diastolic rumbling murmurs, with a presystolic accentuation caused by atrial contraction. Continuous murmurs begin some time in systole and spill into diastole (they have S_2 in their 'body') as the gradient between the two chambers or vessels exists in both systole and diastole. Examples include patent ductus arteriosus, arteriovenous fistulae (coronary, pulmonary or peripheral) and the rupture of an aortic sinus of Valsalva aneurysm into the right atrium. The murmurs of aortic or pulmonary regurgitation are diastolic and decrescendo, as the gradient diminishes towards end-diastole. The effect of the various physiologic maneuvers on different cardiac murmurs is displayed in Table 12.2.

Table 12.2 Effects of physiological maneuvers on auscultatory events

Maneuver	*Major physiological effects*	*Useful auscultatory changes*
Respiration	↑ venous return with inspiration	↑ right heart murmurs and gallops with inspiration, splitting of S_2
Valsalva (initial ↑ BP, phase I; followed by ↓ BP, phase II)	↓ BP, ↓ venous return, ↓ LV size (phase II)	↑ HOCM ↓ AS, MR MVP click earlier in systole, murmur prolongs
Standing	↓ venous return ↓ LV size	↑ HOCM ↓ AS, MR MVP click earlier in systole, murmur prolongs
Squatting	↑ venous return ↑ systemic vascular resistance ↑ LV size	↑ AS, MR, AR ↓ HOCM MVP click delayed, murmur shortens
Isometric exercise (e.g. hand grip)	↑ arterial pressure ↑ cardiac output	↑ gallops ↑ MR, AR, MS ↓ AS, HOCM
Post PVC or prolonged RR interval	↑ ventricular filling ↑ contractility	↑ AS little change in MR

HOCM = hypertrophic obstructive cardiomyopathy
AS = aortic stenosis
MR = mitral regurgitation
MVP = mitral valve prolapse
AR = aortic regurgitation
MS = mitral stenosis
↑ = increased intensity; ↑ = decreased intensity
PVC = premature ventricular contraction

12.2 Approach to a patient with cardiovascular disease

Approach to a Patient with Chest Pain

Chest pain is one of the commonest complaints encountered by the physician. Elucidation of the etiology of chest pain is complicated by the fact that several thoracic structures share afferent pain fibre pathways. Thus, the heart, great vessels, hilar structures, the esophagus, pleura and thoracic musculoskeletal tissue transmit pain afferents to the same spinal segments.

Table 12.3 Causes of chest pain

1. Cardiac
   - myocardium (ischemia, infarction, myocarditis, hypertrophic cardiomyopathy, aortic stenosis, aortic regurgitation)
   - pericardium (pericarditis)
2. Great vessels
   - aortic dissection
   - aortic aneurysm
   - pulmonary embolism
3. Pulmonary
   - pleuritis (with or without pneumonia)
   - pneumothorax
4. Gastrointestinal
   - esophageal spasm
   - gastric reflux
   - peptic ulcer disease
   - biliary tract disease
5. Neuromuscular
   - herpes zoster
   - compressive lesions of the spinal roots
6. Miscellaneous
   - costochondritis
   - mediastinal tumour
   - rib fracture

Causes The causes of chest pain and the tissue of orgin are listed below. A careful history often helps in differentiating the exact etiology of chest pain (Table 12.3).

Clinical features Myocardial ischemia may produce chest pain, usually related to the atherosclerotic obstruction of one or more coronary arteries. The term *angina pectoris* is used to refer to brief episodes of chest pain due to myocardial ischemia. The patient may describe the sensation as 'pain', 'tightness', 'heaviness' or an 'uneasiness' in the chest. It is useful to ask the patient to point to the area of discomfort and indicate its extent. Angina is usually in the retrosternal area and the size of the area is that of the closed fist or greater. Discomfort localised to the tip of a finger is unlikely to represent angina. The discomfort may be felt in the throat, mandible and may radiate along the ulnar aspect of either arm, usually the left. Pain above the mandible or below the umbilicus is unlikely to be anginal. Anginal episodes typically last from a minute to ten minutes in duration; momentary pain or pain lasting for several hours is most likely non-anginal. Angina is typically precipitated by effort such as walking or climbing stairs. Two important but neglected features of angina are its *reproducibility* (the patient identifies the chest pain under the same circumstances) and the *gradation of effort* (angina occurs when a certain level of energy is expended but lower degrees of effort are symptom-free). Angina

may be precipitated by *emotions* such as anger or sorrow, or even exposure to the cold. It is usually relieved by cessation of the precipitating activity or removal of the precipitating factor; nitroglycerin typically relieves pain in less than 10 minutes. Physical examination reveals an elevation in the heart rate and systolic blood pressure product ('double product').[1] An audible fourth heart sound denotes altered myocardial compliance. Some patients may have transient systolic murmurs that arise due to ischemia-induced papillary muscle dysfunction and consequent mitral regurgitation.

A classification of angina pectoris is provided below. This classification of angina pectoris has been recommended by the Canadian Cardiovascular Society and has replaced the New York Heart Association's classification, which was abandoned in 1973.

Classification of angina pectoris

1. angina with strenuous or rapid or prolonged exertion at work or recreation. Ordinary physical activity such as walking and climbing stairs does not cause angina.
2. slight limitations of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair-climbing after meals, or in the cold, or in the wind, or under emotional stress, or only during the few hours after waking. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
3. marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.
4. inability to carry on any physical activity without discomfort; an anginal syndrome may be present at rest.

Occasionally, episodes of myocardial ischemia occur without chest pain but with episodic dyspnea or exhaustion. These symptoms are referred to as *anginal equivalents.* The predictive value of these symptoms for myocardial ischemia is less than that of chest pain. *Variant angina* is another subset where chest pain occurs periodically at rest, and is often nocturnal; it is related to coronary spasm superimposed over coronary atherosclerosis.

[1] Double product is a correlate of myocardial oxygen consumption.

When chest pain which is anginal in character lasts for more than 15 minutes, it represents prolonged myocardial ischemia. Two common causes are *coronary insufficiency without infarction* and *acute myocardial infarction.* The chest pain of myocardial infarction is more severe and is associated with sweating, nausea and vomiting. Precordial palpation may reveal a late systolic bulge, as well as the palpable correlate of a fourth heart sound. An apical systolic murmur denoting papillary muscle dysfunction is frequent. The electrocardiogram shows ST segment elevation or depression along with T wave changes.

The pain of *aortic dissection* resembles that of myocardial infarction but is more intense, sharper, has a tearing component and may migrate to the interscapular area with extension of dissection. When the patient has Marfan syndrome and the peripheral pulses are asymmetrical and a murmur of aortic regurgitation is audible, the diagnosis is obvious.

A large pulmonary embolus may cause chest pain very much like acute myocardial infarction. The presence of associated tachypnea, a history of hemoptysis and a source of embolus in the legs (deep venous thrombosis) suggest the diagnosis. A definitive diagnosis may require a ventilation-perfusion scan and a pulmonary angiogram.

The pain of *pericarditis* has two components: the sharp, more left-sided component is exacerbated by respiratory movement, postural change and sometimes by swallowing. The second component is a dull retrosternal ache. The pain of pericarditis often radiates to the trapezius ridge and is lessened by leaning forward. A triphasic or biphasic pleuropericardial rub may be audible. The electrocardiogram often shows diffuse ST segment elevation without concomitant T wave changes and the chest radiograph may reveal enlargement of the cardiac silhouette. An echocardiogram may identify a percardial effusion, which further supports the diagnosis.

Pleural pain due to pleuritis may mimic pericardial pain but attention is directed to this etiology by the presence of a pleural effusion. The most important characteristic is the exacerbation of chest pain by deep inspiration or cough. A spontaneous *pneumothorax* can cause chest pain but dyspnea is an important associated feature. A chest radiograph is diagnostic.

Acute *mediastinitis* (due to tuberculosis, other infections or esophageal rupture) can cause severe chest pain which radiates to the back. Mediastinal emphysema also presents with severe chest pain; the presence of the characteristic crepitus synchronous with the heart beat and the presence of mediastinal air in the chest radiograph suggest the diagnosis.

Gastroesophageal reflux is also a common cause of chest discomfort which is substernal or epigastric in location. It may resemble angina or may be of a burning nature. Further difficulty in the diagnosis arises due to the observation that esophageal pain may be relieved by the smooth muscle relaxant action of nitroglycerin. Chest pain provoked by eating large meals, or by assuming a recumbent posture after meals and which is relieved by standing or with antacids suggest the diagnosis. A barium cine-esophagogram is required to confirm the diagnosis.

The pain of *peptic ulcer* may mimic angina but often tends to be gnawing, aching or boring and is relieved by food. Biliary colic may also mimic angina but episodes tend to be longer, more severe and there is usually an abdominal component in the right hypochondrium.

The discomfort of *costochondritis* can be sharp or dull and can be worsened by chest movement. Occasionally there may be an obvious swelling of the costochondral junction (*Tietze syndrome*). Chest pain may be reproduced by direct pressure on the costochondral joint.

Rarely, disease of the cervical and thoracic vertebrae may cause diagnostic confusion. Compression of dorsal nerve roots by a herniated intervertebral disc usually causes a sharp, brief and shooting pain; compression of ventral roots may cause dull and gnawing pain. Root pain is usually made worse by movement, cough or even by sneezing.

In many patients with chest pain, a cause is not evident despite extensive investigations. Some of these patients suffer from an anxiety state known as *cardiac neurosis.*

Approach to a Patient with Dyspnea

Dyspnea is defined as a subjective, uncomfortable awareness of breathing. A number of mechanisms operate to mediate this sensation. These include receptors in the lungs, upper airways, respiratory muscles and central respiratory centres. The patient's awareness originates in the cerebral cortex.

Etiology The common causes of dyspnea are listed in the Table 12.4.

Clinical features The most common causes of dyspnea are heart failure and pulmonary disease. Dyspnea during exertion is an early symptom of left ventricular failure. Initially, it occurs with moderate to severe degrees of exertion but as ventricular dysfunction progresses, lower degrees of exertion can result in symptoms. In mitral valve disease, dyspnea reflects raised left atrial pressures, while left ventricular function is preserved.

Cardiac dyspnea is related to pulmonary capillary hypertension; pulmonary congestion stimulates respiration by way of the Hering-Breuer reflex mediated by the vagus nerve. The cardiac disease may be valvular heart disease, coronary artery disease or cardiomyopathy. A chest radiograph and an echocardiogram yield valuable clues to the etiology of cardiac dyspnea.

Acute pulmonary edema results from a severe degree of pulmonary capillary congestion that results in exudation of fluid into the lung interstitial spaces and into the alveoli. Common precipitating factors include sudden increases in

Table 12.4 Causes of dyspnea

Acute dyspnea	*Chronic dyspnea*
Cardiac • acute left ventricular failure (valve disease, ischemia, severe hypertension, excerbation of myocardial disease, myocarditis) • acute pericarditis • pericardial effusion with tamponade	**Cardiac** • pulmonary venous hypertension (valve disease, cardiomyopathies, cardiac shunt lesions) • pulmonary arterial hypertension primary pulmonary hypertension cor pulmonale • pericardial effusion • angina equivalent
Pulmonary • exacerbation of COPD • acute asthma • pneumonia • pulmonary embolism • pneumothorax • pleuritis with effusion • pulmonary collapse	**Pulmonary** • COPD • interstitial lung disease • pleural effusion • post-pneumonectomy • postinfectious pulmonary fibrosis • neoplasms
Others • upper airway obstruction • toxic gas inhalation • hypoxemia (sudden exposure to high altitude, severe blood loss) • anaphylactic reaction • conversion reaction	**Others** • chronic severe anemia • conversion reaction • diseases of the chest wall and respiratory muscles

COPD = Chronic obstructive pulmonary disease

blood pressure, arrhythmias, infections or severe ischemia in a person with preexisting cardiac disease. The patient with pulmonary edema is easy to recognise as he would be sitting upright, and appears tachypneic and diaphoretic. The skin is cold and clammy, reflecting peripheral vasoconstriction due to sympathetic overactivity. The sputum may be pink and frothy. Auscultation of the lungs reveals bilateral bubbling rales, rhonchi and wheezes. These episodes are sometimes referred to as *cardiac asthma.*

Orthopnea is a form of dyspnea in which the patient must sit upright to avoid respiratory distress. She may lie on several pillows or sit on the side of the bed with legs hanging down. Orthopnea is a manifestation of severe pulmonary venous congestion. The sitting posture affords relief due to the redistribution of blood to the legs and due to lowering of the diaphragm (which increases vital capacity).

Paroxysmal nocturnal dyspnea is the occurrence of nocturnal episodes of dyspnea, usually after two hours of retiring to bed. The patient feels 'out of breath' and may go up to a window to breathe in fresh air. The attacks may be short-lived or may last for a couple of hours before subsiding. Episodes occur at night because the fluid shifts from the lower extremities to the pulmonary capillaries due to the recumbent posture.

A classification of cardiac dyspnea formulated by the New York Heart Association (NYHA) is provided below.

Cheyne-Stokes respiration is a type of periodic breathing in which periods of apnea alternate with periods of hyperpnea. It can be seen in advanced cardiac failure, although it is more

Functional classification* of cardiac symptoms (NYHA)

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in the inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

* This classification is now used to categorise the patient's symptoms of heart failure; angina pectoris is classified and categorised according to the guidelines created by the Canadian Cardiovascular Society.

often encountered in patients with diseases of the central nervous system (brainstem), narcotic use and in some subjects, at a high altitude.

Episodes of pulmonary edema in a patient with a prosthetic valve should arouse suspicion of valve malfunction (such as regurgitation or thrombotic obstruction). A history of dyspnea only when the patient sits up or is in a particular position should lead to suspicion of a ball-valve atrial thrombus or an atrial myxoma. Dyspneic episodes in a cyanotic child that are relieved by squatting, points to the possibility of Fallot's tetralogy.

Obstructive disease of the airways is a common cause of dyspnea. Obstruction of intrathoracic airways as in asthma results in acute episodes of breathlessness commonly known as asthmatic wheezing. The dyspneic patient has an audible wheeze, and the use of accessory muscles of respiration is conspicuous. In severe cases, there may be cyanosis and this usually indicates an emergency. Pulmonary function tests and a chest radiograph are useful for ascertaining the presence and the severity of airway obstruction.

The clinical differentiation of *bronchial asthma* from cardiac asthma can be difficult. A first attack of so-called asthma in a middle aged or elderly individual should be viewed with suspicion and a cardiac cause excluded carefully. A prior history of heart disease, the presence of pulsus alternans, a reduced proportional pulse pressure (which is defined as [systolic blood pressure – diastolic blood pressure ÷ systolic blood pressure] that is less than 0.25), an abnormal blood pressure response to the Valsalva maneuver (such as the absence of overshoot of blood pressure or a square wave response), and the presence of jugular venous distension at rest or during the abdominojugular test are four highly specific bedside signs of ventricular dysfunction that suggest a cardiac etiology of dyspnea. A prior history of pulmonary disease favours a pulmonary cause of dyspnea.

Chronic bronchitis and emphysema are also associated with exertional dyspnea; a history of chronic cough with expectoration of muco-purulent sputum suggests the diagnosis. Diffuse pulmonary parenchymal disease (of varied etiology) can result in dyspnea as can disease of or weakness of the respiratory muscles.

Acute dyspnea of pulmonary origin may arise due to a spontaneous pneumothorax or acute pulmonary embolism. These conditions are discussed in detail in the section on respiratory disease.

Occasionally, episodes of acute dyspnea are associated with hyperventilation, clear lungs, and signs of tetany (such as, tingling around the mouth, positive Chvostek's sign[1] and spasm of

muscles of hand). These signs usually indicate that dyspnea is part of *anxiety attacks.*

Approach to a Patient with Edema

Edema refers to an accumulation of interstitial fluid in excess of the normal amount. For clinical purposes, this increase of fluid must be of a degree that renders it clinically detectable.

Pathophysiology and etiology Edema develops when the capillary hydrostatic pressure exceeds that of the tissues, when the plasma colloid oncotic pressure of the plasma is less than that of the tissues, when there is an abnormal permeability of the capillaries or when the lymphatic drainage of an area is impaired. The specific causes of edema are listed below.

Clinical features Edema may be clinically silent but manifests initially as mild gain in weight or tightening of rings or of footwear. With greater degrees of fluid accumulation, edema becomes clinically apparent. Edema may be pitting or non-pitting. Lymphatic edema is generally non-pitting whereas edema related to elevated venous pressure is usually pitting. Edema related to accumulation of abnormal interstitial material such as mucopolysaccharides is seen in thyroid disease, is prominent especially over the shins, and tends to be non-pitting. Edema may be *localised* or *generalised.* When localised, edema may be uni- or bilateral. Bilateral edema of dependent parts, although localised, often has a systemic cause. Bilateral edema of the legs may be due to raised venous pressure, prior deep venous thromboses, prolonged inactivity, or due to a systemic disease associated with hypoalbuminemia. Sometimes edema may be transient and related to premenstrual fluid accumulation in women. *Unilateral localised edema* often points to a local pathology. Unilateral edema of a paralysed extremity is common in stroke patients. Edema of an arm after radical breast surgery points to an interference with the venous or lymphatic drainage of the arm; this may be related to metastatic disease or venous thromboses.

Table 12.5 Causes of edema

A. Generalised edema

Increased venous pressure
- Congestive heart failure
- Constrictive pericarditis
- Excessive infusion of fluids
- Anemia
- Beri-beri

Reduced serum protein
- Nephrotic syndrome
- Liver disease
- Malabsorption
- Malnutrition

Altered fluid excretion
- Renal failure
- Pregnancy
- Premenstrual period
- Steroids

Altered capillary permeability
- Angioneurotic edema
- Snake bite
- Drugs

B. Localised edema

Increased venous pressure
- Venous obstruction
- Varicose veins
- Prolonged recumbency of a part

Increased capillary permeability
- Insect or animal stings
- Allergies
- Exposure to heat, cold or other irritants
- Injury or fractures
- Cutaneous infections

Lymphatic obstruction
- Filariasis
- Prior surgery
- Metastatic disease
- Prior inflammation

Accumulation of subcutaneous deposits
- Hypothyroidism

[1] Tapping of the masseter with a finger results in spasm of the muscle.

Edema and atrophy of the skin overlying a fractured bone is termed *Sudek's atrophy* and is associated with rarefaction of the underlying bones. Edema of the upper half of the body should lead to suspicion of superior vena caval thrombosis or obstruction, often due to malignant intrathoracic pathology. Edema of the lower half of the body may indicate inferior vena cava obstruction. Edema of a leg is frequent after groin dissection procedures for removing lymph nodes. Painful edema of a calf may indicate phlebitis of the calf veins.

The clinical history must include an enquiry into the rapidity of onset of edema and other antecedent events (such as surgery). The clinical examination must include an assessment of the extent and distribution of edema. It is important to remember that in the recumbent patient, edema first develops in the presacral region. A detailed enquiry must be made about the presence of cardiac, hepatic or renal disease especially when the edema is generalised; these three causes are among the commonest causes of generalised edema.

Investigations should include routine hematologic tests, blood biochemistry (including blood sugar, urea, creatinine, albumin and other liver function tests), and urinalysis for checking urinary protein. A chest X-ray may indicate cardiac disease (congestive heart failure) or any other intrathoracic pathology. In the case of localised edema of venous or lymphatic origin, a venogram or a lymphangiogram may be indicated.

Treatment The treatment of edema depends on the underlying etiology; these are discussed under the individual categories. Generally diuretics are effective in treating edema related to increased hydrostatic pressure. Avoidance of prolonged recumbence and tight-fitting clothes (that interfere with venous flow) are other useful adjuncts. Reduced serum protein may require enteral or parenteral nutritional supplementation.

Approach to a Patient with Palpitations

Palpitations are an uncomfortable awareness of the heartbeat. This symptom is frequent and is associated with benign and functional disturbances as well as with serious ailments.

Pathophysiology and etiology Palpitations are related to an alteration in heart rate, rhythm, force of cardiac contraction, stroke volume or an altered perception of a normal beat. Anxiety is one example where there is an abnormal perception of normal cardiac motion. Hyperadrenergic states are associated with palpitations related to catecholamine excess; palpitations may be transient or sustained. Transient palpitations may occur with states such as fever, fear or apprehension. Palpitations are a feature of hyperthyroidism, anemia and pheochromocytoma. Palpitations may be related to the intake of tea, coffee, tobacco or other xanthine derivatives such as aminophylline. An altered stroke volume is the basis of palpitations in patients with aortic or mitral regurgitation, ventricular septal defect and hyperkinetic circulatory states (conditions associated with a high cardiac output). Rhythm disorders are associated with palpitations related to both cardiac rate and altered stroke volume. An extrasystole is associated with palpitation related to a larger stroke volume of the postextrasystolic beat due to an increase in ventricular filling time as a result of the compensatory pause.

Clinical features and investigations Clues to the etiology of palpitation are often obtained by carefully eliciting the history. A careful inquiry into situations (including drug intake), which provoke palpitations, is important. Occasional 'skipped beats' are due to extrasystoles. Palpitations which occur only during left-sided recumbency are often related to an increased stroke volume which is more apparent in this position when the heart closely approximates the

In supraventricular tachycardia, the palpitations are sudden in onset and offset, and are regular. When palpitations are sudden in onset but are irregular, atrial fibrillation may be the underlying etiology. Ventricular tachycardia is not usually associated with palpitations as the cardiac output is significantly reduced. Slow forceful palpitations associated with brief periods of light-headedness or syncope may direct attention to second or third-degree atrioventricular block with a slow ventricular rate. A gradual onset of tachycardia with exercise or stress suggests sinus tachycardia. The rate of the tachycardia yields additional clues. A rate of over 160 beats per minute indicates supraventricular tachycardia (except in infants and young children). A rate between 100–140 beats per minute indicates sinus tachycardia. A slow heart rate may indicate a disturbance of the atrioventricular conduction system. The presence of heat intolerance, thyromegaly, warm, moist extremities, and tremors may indicate thyroid disease. Several of these features are present in a generalised anxiety state but the palms of the hand are typically cold and the clinical picture yields additional clues. Clinical examination may also reveal a regurgitant murmur, significant anemia or other features of an underlying hyperkinetic state such as a wide pulse pressure, warm extremities, or basal systolic murmurs.

An electrocardiogram obtained during an episode of palpitations is invaluable in establishing a diagnosis in patients who report bouts of palpitations. In patients with episodic irregular palpitations, an ambulatory ECG recording may reveal ventricular or atrial extrasystoles. Evaluation for thyroid or adrenal hormone excess may be indicated when other common causes are excluded.

Treatment The treatment of palpitations depends on the underlying cause of the symptoms. Beta-blockade may be helpful in subjects with sinus tachycardia, especially that related to anxiety or activity. Avoidance of provocative drugs or medication may be helpful. The specific etiology such as valve disease, thyroid disease or rhythm disturbances, must be treated.

Approach to a Patient with Syncope

Syncope is defined as a sudden transient loss of consciousness accompanied by an inability to maintain postural tone.

Etiology and pathophysiology The causes of syncope are enumerated in Table 12.6. The common underlying mechanism, irrespective of the etiology, is reduced blood flow to the brain and consequent loss of consciousness. Under normal conditions, the cerebral blood flow is autoregulated over a range of mean arterial pressures ranging from 50–150 mmHg. When cerebral perfusion pressure drops below 50 mmHg syncope results. The commonest category of disorders which result in syncope is abnormal cardiovascular autonomic control. Of the various causes listed, the commonest is the *vasovagal* or *vasodepressor syncope.* It is also referred to as the common faint. This occurs in otherwise healthy individuals subjected to a variety of precipitating factors which modify the normal cardiovascular autonomic responses. These factors include extreme heat, pain, hunger, alcohol intake or prolonged recumbency. There are two components of this condition: the *cardio-inhibitory component,* that is, reflex heart slowing or the development of high-grade atrioventricular block, and the *vasodepressor component,* that is, inappropriate peripheral vasodilatation. The syndrome results from an initial sympathetic activation which results in tachycardia and vigorous ventricular contractions that paradoxically activate inhibitory vagal afferent ventricular receptors. This culminates in reflex bradycardia, diaphoresis, pupillary constriction, lightheadedness and finally syncope.

Orthostatic syncope is common in elderly

Table 12.6 Causes of syncope

A. *Abnormalities of autonomic cardiovascular control*
1. Vasodepressor or vasovagal syncope
2. Orthostatic or postural syncope
3. Primary autonomic insufficiency
   preganglionic
   postganglionic
4. Secondary autonomic insufficiency (diabetes, amyloidosis, alcoholism, syphilis, central nervous system disorders such as Shy-Drager[1] syndrome and Parkinson's disease)
5. Miscellaneous situational factors
   carotid sinus syncope
   micturition syncope
   tussive or cough syncope
   defecation syncope
   neuralgia-related syncope

B. Cardiac syncope

1. Obstruction to ventricular inflow or outflow
   aortic stenosis
   hypertrophic obstructive cardiomyopathy
   atrial myxoma or ball valve thrombus[2]
   prosthetic mitral or aortic valve thrombosis
   pulmonic stenosis
   tetralogy of Fallout
   pulmonary embolism
2. Arrhythmic syncope
   bradyarrhythmias (complete heart block or sick sinus syndrome)
   tachyarrhythmias
   - ventricular
   - supraventricular

C. *Metabolic*
   hypoglycemia
   hypocapnia (hyperventilation syndrome)

D. *Miscellaneous*
1. Vertebrobasilar insufficiency

[1] Shy-Drager syndrome is a neurologic disorder characterised by postural hypotension.
[2] Ball valve thrombus refers to a spherical intracavitary clot.

subjects especially when they are on antihypertensive agents such as alpha blockers, diuretics or calcium channel blockers, and after episodes of diarrhea, vomiting, hemorrhage or any other condition predisposing to volume depletion. Occasionally, syncope is precipitated in individuals with *hypersensitive carotid sinus* by the wearing of a tight collar or while shaving. *Situational syncope* can arise during micturition, after defecation, or after a bout of cough. The subject performs a Valsalva maneuver involuntarily during these events and this leads to a reduced venous return. Subjects with left or right ventricular inflow or outflow obstruction (of whatever etiology) are also susceptible to syncope. Syncope in these subjects is often exertional when reflex-mediated dilatation of the peripheral arterial beds occurs in the setting of a failure to increase arterial pressure or cardiac output. Complete heart block is the most common cardiac cause of syncope. In this condition a transient or irreversible interruption of atrioventricular conduction results in a subsidiary pacemaker taking over as the escape focus. An inadequate rate of the subsidiary focus can result in inadequate cardiac output and cerebral hypoperfusion with consequent syncope. Ventricular tachycardia and fibrillation are typically associated with syncope and a risk of sudden death. Subjects with a long electrocardiographic QT interval are also susceptible to a polymorphic ventricular tachycardia that can result in syncope. Tachyarrhythmias of atrial origin do not usually cause syncope in the absence of an accessory bypass tract because the atrioventricular node restricts ventricular rate by limiting the number of impulses that conduct through it.

Diagnostic approach A proper history is the most important step in the evaluation of the subject with syncope. An enquiry is made about the posture of the subject, preceding events and circumstances, and the temporal course of onset and recovery. Fainting in the supine posture should always raise suspicion of a seizure rather than a syncope, though complete heart block and tachyarrhythmias can cause syncope regardless of the posture. Temporal lobe seizures are the most likely to be confused with

syncope but must be suspected whenever there are associated repetitive motor movements, sensory hallucinations, or if there is a prolonged confusional state after the event.[1] An enquiry should be made about the presence or absence of premonitory symptoms which are more common in seizures but can be seen in bradyarrhythmia-related syncope. The presence of a well-defined neurologic abnormality, such as paresis or dysarthria, suggests a cerebrovascular event rather than a syncope. Repeated multiple episodes without physical injury and in the presence of observers or dramatic situations in an individual behaving unusually should point to the likelihood of hysterical faints. Light-headedness occurring repeatedly 1–2 hours after meals may point to reactive hypoglycemia, which is often an early symptom of diabetes mellitus.

Physical examination must include an assessment of postural changes in blood pressure and heart rate, a search for vascular (carotid) bruits and a careful examination of the heart for the presence of murmurs, rubs and gallops. Carotid sinus pressure may be applied in a monitored situation such as in an ICU for evaluating for a hypersensitive carotid sinus.

Among the investigations, an ECG is probably the most useful test. Though it can demonstrate the presence of bradyarrhythmia or tachyarrhythmia, it often yields indirect clues such as the presence of a bifascicular block which may suggest the need for further evaluation. The presence of a long QT interval may point to the need for evaluation for ventricular arrhythmias as may the electrocardiographic presence of Q waves indicating a prior myocardial infarction which might provide an arrhythmic substrate. Ambulatory ECG monitoring is likely to yield results in subjects with frequent episodes of syncope when correlation between ECG findings and clinical symptoms can be sought.[2] The appropriate duration of monitoring is at least 24 hours. The *signal-averaged ECG* is a newer method of investigating the likelihood of ventricular tachycardia being a cause of syncope. The technique utilises the high frequency, low amplitude signals in the terminal portion of the QRS complex known as *late potentials,* which are not evident on the standard ECG. The absence of late potentials helps to identify subjects with a low incidence of ventricular tachycardia. The echocardiogram is important for the exclusion of cardiac pathology such as valvular aortic stenosis, hypertrophic obstructive cardiomyopathy or a myxoma. The likelihood of a bradyarrhythmia-related syncope may necessitate invasive electrophysiologic testing to gain information about the sinus node, atrioventricular node conduction, the infrahisian[3] conduction system and the presence of inducible ventricular arrhythmias. In subjects with all other investigations negative, the *tilt table test* may be used to detect susceptibility to vasodepressor syncope. The subject is held upright on a tilt table at an angle of 60–80 degrees for 15 minutes to an hour. In subjects with vasodepressor syncope, the episode may be reproduced during the tilt test. A routine electroencephalogram may have a poor yield in the investigation of syncope unless there are features in the history to suggest a seizure disorder.

Prognosis The prognosis of subjects without a cardiac cause of syncope is excellent (one year mortality 0–5%), whereas that of subjects with a cardiac cause is more ominous (one year mortality 20–30%).

Treatment The treatment of syncope is based on the underlying etiology. Permanent pacemaker implantation may be beneficial in patients with a proven bradyarrhythmic cause of syncope

[1] Postsyncopal confusion in subjects with ventricular arrhythmias rarely lasts for more than 30–60 seconds.

[2] In patients with arrhythmia-related syncope there is a fair correlation in general (25–50%) between ECG findings and clinical symptoms.

[3] Infrahisian means below the bundle of His.

and in subjects with a hypersensitive carotid sinus. Antiarrhythmic drugs are indicated in tachyarrhythmia-related syncope. Orthostatic hypotension if identified should be treated and valvular heart disease managed by appropriate surgical procedures. Neuralgia-related syncope may benefit from therapy with carbamazepine.

Approach to a Patient with Postural Hypotension

Postural hypotension is defined as a fall of 20 mmHg or more in systolic blood pressure when the subject changes from a recumbent to an upright position.

Etiology and pathophysiology Normally the blood pressure is maintained within a narrow range by neural control mechanisms. Pressure sensors located in the aortic arch and carotid sinus relay information to the central nervous system, which in turn relays impulses to the splanchnic and peripheral vascular bed. Failure of either the afferent or the efferent limb of this reflex arc can lead to an inability to adjust the blood pressure to postural change. The normal circulatory response to standing is an increase (5%), or no change (60%), or a decrease, of less than 10 mmHg (35%) in systolic pressure. The diastolic pressure may rise (50%), or not change (40%), or fall by upto 4 mmHg (10%). The causes of postural hypotension are listed in Table 12.7.

Table 12.7 Causes of postural hypotension

A. *Diminished plasma volume*
   1. Hemorrhage (internal or external)
   2. Diuretic therapy
   3. Gastrointestinal volume losses (diarrhea or vomiting)
   4. 'Third space' losses (peritonitis, pancreatitis)
   5. Diabetes mellitus
   6. Addison's disease
   7. Heat disorders

B. *Diminished forward cardiac output*
   1. Valvular heart diseases (valve stenosis)
   2. Myocardial diseases
   3. Arrhythmias

C. *Impaired neurocirculatory reflexes*
   1. Old age
   2. Parkinson's disease
   3. Polyneuropathies
      - Diabetes mellitus
      - Alcohol
      - Guillain-Barre syndrome
   4. Central nervous system lesions
      - Spinal cord lesions above T6 spinal level
      - Brainstem lesions
      - Certain cortical lesions
   5. Other neurologic diseases
      - Neurosyphilis
      - Primary autonomic degeneration
      - Multiple system degeneration
      - Familial dysautonomia (Riley-Day syndrome)

Clinical approach The common symptoms of postural hypotension are transient dizziness and blurred vision on changing from a recumbent to an erect posture. If the fall in systolic pressure is profound, cerebral hypoperfusion can result in collapse or unconsciousness. When symptoms such as those described above are related to changes in posture, an enquiry is made about the use of any drugs. Diuretics can deplete plasma volume and thereby cause a malfunction of the postural reflexes. Drugs which depress cardiac output or interfere with neural reflexes (ganglion-blockers, alpha adrenergic-blockers, drugs which cause peripheral neuropathy, and sedatives) can result in postural hypotension. A history of events which result in volume depletion such as hemorrhage, diarrhea or excessive vomiting must be sought. Diabetes mellitus can result in volume depletion if blood sugar control is poor. A history of salt-craving or abnormal pigmentation of skin creases may arouse suspicion of Addison's disease. Several neurologic diseases can affect the central sympathetic outflow or the postganglionic nerves and thereby impair normal autonomic

regulatory reflexes.

Physical examination must begin with a careful record of blood pressure in supine, sitting and standing positions. It is preferable to have the subject recumbent for about 10 minutes and to check the blood pressure at 10 seconds, 2 minutes and 4 minutes after standing. Once a significant postural drop in blood pressure is confirmed, a careful examination is conducted to detect other signs of depletion of intravascular volume (such as skin turgor, neck veins or pallor), signs of a diminished, cardiac output (such as feeble or irregular pulse, S_3 gallop or chest rales), or signs of an endocrinopathy (diabetes mellitus or Addison's disease). A careful neurologic examination is mandatory to exclude peripheral neuropathies, extra-pyramidal disorders, cortical or brainstem disease and autonomic dysfunction. The presence of abnormal sweating patterns and abnormal pupillary responses[1] are important clues to the presence of autonomic disturbances.

Approach to a Patient with Hypotension or Shock

Hypotension may be defined as the physical finding of a blood pressure reading below the usual range of blood pressure for that individual. Due to the wide variation in blood pressure from person to person (interindividual variation) and also due to the fact that an individual's blood pressure varies from day to day and, in fact, from hour to hour (intraindividual variation), no absolute level can be determined which can be called normal and below which a person is said to be hypotensive. Thus, a blood pressure level of 90/60 mmHg in an asymptomatic, thin, young woman may be normal for her. However, by and large, a supine systolic blood pressure of 85 or 80 mmHg measured with a proper sized pneumatic cuff may be considered abnormal.

Shock is a clinical syndrome of inadequate tissue perfusion secondary to circulatory failure. Thus hypotension may exist without evidence of shock, and shock (especially in its early stages) may exist with a reasonable preservation of arterial pressure.

Etiology An etiologic classification of shock is shown in Table 12.8. Arterial pressure is determined by the product of stroke volume (SV), heart rate (HR) and systemic vascular resistance (SVR) according to the equation

$$\text{Mean arterial pressure} = SV \times HR \times SVR.$$

Thus, arterial hypotension can result from the alteration of any one of the terms in the equation. Shock that results from a decrease in peripheral vascular resistance is referred to as distributive or veno-vasodilatory shock. In this condition there is marked venous and arteriolar dilatation which results in a redistribution of central blood volume to the periphery consequent to the increased vascular capacitance. These patients often have physical findings of a warm, flushed, dry skin despite the presence of shock: this is known as *warm shock*. The classical examples of this situation are septic shock and anaphylactic shock. A shock state caused by a reduction in intravascular volume is referred to as *hypovolemic shock*. Depletion of intravascular blood volume by 25 per cent or more in a normal individual results in shock. Shock states resulting from cardiac pump failure are grouped together under the category of *cardiogenic shock*.

Pathophysiology and clinical features As the systolic pressure falls to a level of 60–70 mmHg, cerebral and renal vascular autoregulatory mechanisms begin to fail with consequent under perfusion of the brain and the kidneys. When the diastolic blood pressure falls below 60 mmHg, coronary perfusion is reduced. Reduced cerebral perfusion results in confusion, obtundation, and disorientation. It may culminate in a loss of consciousness if the shock

1 Hyperhidrosis (excessive sweating) with asymmetric pupils are useful signs.

Table 12.8 Etiologic classification of shock

I. Increased vascular capacitance (veno-vasodilatory shock, distributive shock)

A. *Neurogenic*
   1. Spinal cord injury

B. *Septic shock*

C. *Anaphylaxis*

D. *Drugs*
   1. Anesthesia
   2. Sympatholytics
   3. Adrenergic blockers
   4. Venodilators

II. Reduction of intravascular volume (hypovolemic shock)

A. *Loss of blood volume (hemorrhage)*
   1. External loss
      - Trauma
      - Gastrointestinal bleeding
      - Severe hemoptysis
   2. Internal or sequestered blood loss
      - Hemothorax
      - Hemoperitoneum
      - Retroperitoneal hemorrhage
      - Ruptured aortic aneurysm
      - Fractures e.g. of the hip

B. *Loss of plasma volume*
   1. Loss of protein-rich body fluids
      - Burns
   2. Dehydration
      - Gastrointestinal loss
        Vomiting
        Diarrhea
      - Renal loss
        Diabetic ketoacidosis
        Hyperosmolar non-ketotic coma
        Diabetes insipidus
        Adrenal insufficiency
        Overly aggressive diuretic therapy
   3. Internal or sequestered loss
      - Peritonitis
      - Pancreatitis

III. Failure of the heart as a pump (cardiogenic shock)

A. *Impaired systolic performance*
   1. Myocardial injury or depression
      - Myocardial ischemia/infarction
      - Cardiomyopathy
      - Papillary muscle or chordal rupture
      - Ruptured ventricular septum or free wall
   2. Cardiac arrhythmias
      - Marked bradycardia or tachycardia
      - Ventricular fibrillation

B. *Inadequate ventricular diastolic filling*
   1. Extracardiac or extravascular compression
      - Pericardial tamponade
      - Tension pneumothorax
   2. Obstruction to blood flow
      - Pulmonary embolisation
      - Cardiac tumours (e.g. myxoma)
      - Mitral stenosis

C. *Valvular incompetence or malfunction*
   1. Acute severe aortic or mitral valvular regurgitation
   2. Obstruction or incompetence of prosthetic heart valve

is profound or prolonged. Reduced cardiac perfusion results in ischemia, particularly of the subendocardial region. Reduced biventricular function commonly evolves during the course of septic shock which is presumably related to a myocardial depressant factor. Reduced pulmonary perfusion can result in damage to the alveolocapillary barrier; this can result in a loss of surfactant with consequent atelectasis and roentgenologic evidence of alveolar and interstitial infiltrates. Prolonged shock can result in an adult respiratory distress syndrome (ARDS). Renal hypoperfusion results in decreased water and salt excretion which manifests biochemically as elevated blood urea level and clinically as reduced urine output. When severe, shock can result in acute tubular necrosis with consequent acute renal failure. Hypoperfusion of the gastrointestinal tract and the hepatobiliary system can result in gastric stress ulcers, adynamic ileus and icterus. Cutaneous vasoconstriction causes the skin to be cold and

moist, and the skin, lips and nailbeds appear light blue: this is known as acrocyanosis or *cold* shock. The body responds to shock with activation of the sympathetic nervous system with enhanced release of norepinephrine at the free nerve endings and of epinephrine from the adrenal medulla. The renin-angiotensin-aldosterone system is activated with a consequent constriction of systemic arterioles in an attempt to preserve systemic blood pressure. The release of aldosterone results in renal salt and water retention aided by the release of the antidiuretic hormone from the posterior pituitary. The enhanced sympathetic tone causes venoconstriction, thereby augmenting stroke volume and cardiac output.

Diagnostic approach While evaluating the patient with shock in the emergency room, a careful rapid history is combined with immediate therapeutic maneuvers. The insertion of a large bore intravenous cannula (16 gauge) is the first step and oxygen must be administered to any patient who appears clearly hypoxemic. As the intravenous cannula is inserted, blood samples are drawn for appropriate laboratory studies such as hematocrit, hemoglobin, total leucocyte count, serum electrolytes, glucose and urea. A clinical history is obtained rapidly from the patient or the accompanying attendant. A history of trauma points to possible blood loss as the cause of shock. A history of chest pain or dyspnea necessitates the exclusion of coronary artery disease, aortic dissection, pneumonitis, a pneumothorax or a pulmonary embolism as diagnostic possibilities. A history of exposure to any environmental allergen or insect bite is essential to exclude the possibility of anaphylaxis. A careful assessment of the vital signs is mandatory. The pneumatic cuff off the sphygmomanometer must be of the appropriate size and must be deflated slowly as both a small cuff and rapid deflation can cause artifactual elevation of the blood pressure. Even if Korotkoff sounds are inaudible, the systolic pressure can still be estimated by the palpatory method.[1] A good rule of thumb is that a palpable carotid or femoral pulse indicates a systolic pressure of 60 mmHg or more. With hypotension, there is generally a sinus tachycardia due to activation of the sympathetic nervous system. Inappropriate bradycardia must lead to suspicion of intrinsic cardiac conduction system disease, with hypotension resulting from an inadequate cardiac output. A heart rate in excess of 150 beats per minute must alert the clinician to a tachyarrhythmic cause of hypotension.[2] The clinician must, however, remember that a regular appropriate tachycardia may be a ventricular tachycardia (VT). VT causes hypotension by virtue of inadequate diastolic filling, a loss of atrial booster pump function and due to asynchronous ventricular depolarisation. Careful evaluation of the temperature and respiratory rate can also yield clues to the etiology of shock. A rectal temperature must preferably be obtained and a reading in excess of 39.5°C usually indicates sepsis as a cause of hypotension. A rapid respiratory rate with deep breathing defines Kussmaul's breathing; this usually indicates sepsis-associated respiratory alkalosis or a respiratory compensation for an underlying metabolic acidosis such as diabetic ketoacidosis or lactic acidosis. The skin in shock conditions is usually moist, cold and pale except in patients with sepsis. The cardiovascular system must be examined carefully for any murmur: a diastolic murmur of aortic regurgitation might indicate acute aortic dissection or complicated endocarditis of the aortic valve; a systolic murmur may reflect ischemic mitral regurgitation or myocardial infarction with septal rupture.

A careful assessment of the intravascular volume is central to the appropriate treatment of any shock condition. An indirect estimate of

[1] For a description of the palpatory method of measurement of blood pressure refer to section 12.1.

[2] An irregular pulse suggests atrial fibrillation whereas a regular pulse suggests supraventricular tachycardia or atrial flutter.

intravascular volume is provided by a non-invasive estimate of the right atrial pressure obtained by examining the jugular veins. With the patient's neck at an angle of 45 degrees to the trunk, the jugular venous meniscus must be about 4 cm above the clavicle.[1] Failure to appreciate the jugular meniscus in a non-obese subject in whom an adequate examination has been performed would suggest a right atrial pressure less than 5 cmH_2O (4 mmHg) and would, by inference implicate volume depletion as an important factor in the etiology of shock. Prominent engorged neck veins may suggest elevated right atrial pressure and raise the suspicion of cardiac tamponade, pericardial disease, myocardial infarction with right ventricular infarction, pulmonary embolism or cor pulmonale as the possible etiologies of shock.

The abdomen must also be carefully examined in any patient with shock to exclude the possibility of an intraabdominal catastrophe as a cause of shock. The presence of rebound tenderness must alert the physician to the possibility of peritonitis and sepsis. Abdominal distension with preserved bowel sounds must raise the suspicion of retroperitoneal hemorrhage, commonly due to a leaking abdominal aortic aneurysm. A pelvic examination is indicated in women especially when the etiology of shock is unclear; clues to a diagnosis of ruptured tubal pregnancy or sepsis may be detected.

If the subject with shock has an altered sensorium without any localising neurologic findings, 50 ml of 50 per cent dextrose may be infused to treat the possibility of hypoglycemic shock while awaiting laboratory reports of blood sugar. In a diabetic subject, a blood sugar value should be obtained immediately with a dextrometer and urinary ketones estimated qualitatively (Rothera test). The hourly urine output must be meticulously monitored and a urinary catheter must be inserted in the unconscious patient to achieve this objective. A nasogastric tube should be inserted and the gastric contents examined visually for blood in any subject with shock of obscure origin in order to exclude an occult upper gastrointestinal bleed as a cause of shock. The gastric aspirate should also be tested for the *guiac reaction* (for occult blood) and a sample preserved for toxicologic analysis even if there is no gross blood in the aspirate.

If volume depletion is the likely cause of shock, fluid (0.9 N saline) must be rapidly infused. If blood loss is the cause of shock, packed red cells should be infused and the site and cause of blood loss identified and tackled simultaneously. Colloids (plasma substitutes such as dextrans or human serum albumin) may be infused if plasma oncotic pressure is felt to be low because of any reason, or if the volume of infused fluids is to be restricted. In contrast to packed red cells, a major limitation of using crystalloids or colloids is their eventual escape to and equilibration with the extravascular space, especially in patients with a loss of capillary integrity (such as septic shock or ARDS).

If there is no change in the shock state after the infusion of more than 2.5 litres of fluid into the intravascular space, a low dosage of a pressor agent such as dopamine (2–3 μg/kg/min) may be administered. A higher infusion dose may be required in subjects refractory to low doses, especially in septic shock. Norepinephrine bitartrate (0.5–0.2 μg/kg/min) may be required in patients unresponsive to dopamine. In subjects with acute myocardial infarction with shock resistance to volume depletion, a careful consideration must be given to the use of a flow-directed, balloon-tipped pulmonary artery floatation catheter (Swan-Ganz catheter) which can provide a reliable estimate of left ventricular filling pressures and aid in the selection of proper therapeutic measures to

[1] The right atrium is about 5 cm vertically below the sternal angle so that normal right atrial pressure would be 5–10 cmH_2O (approximately 4–8 mmHg).

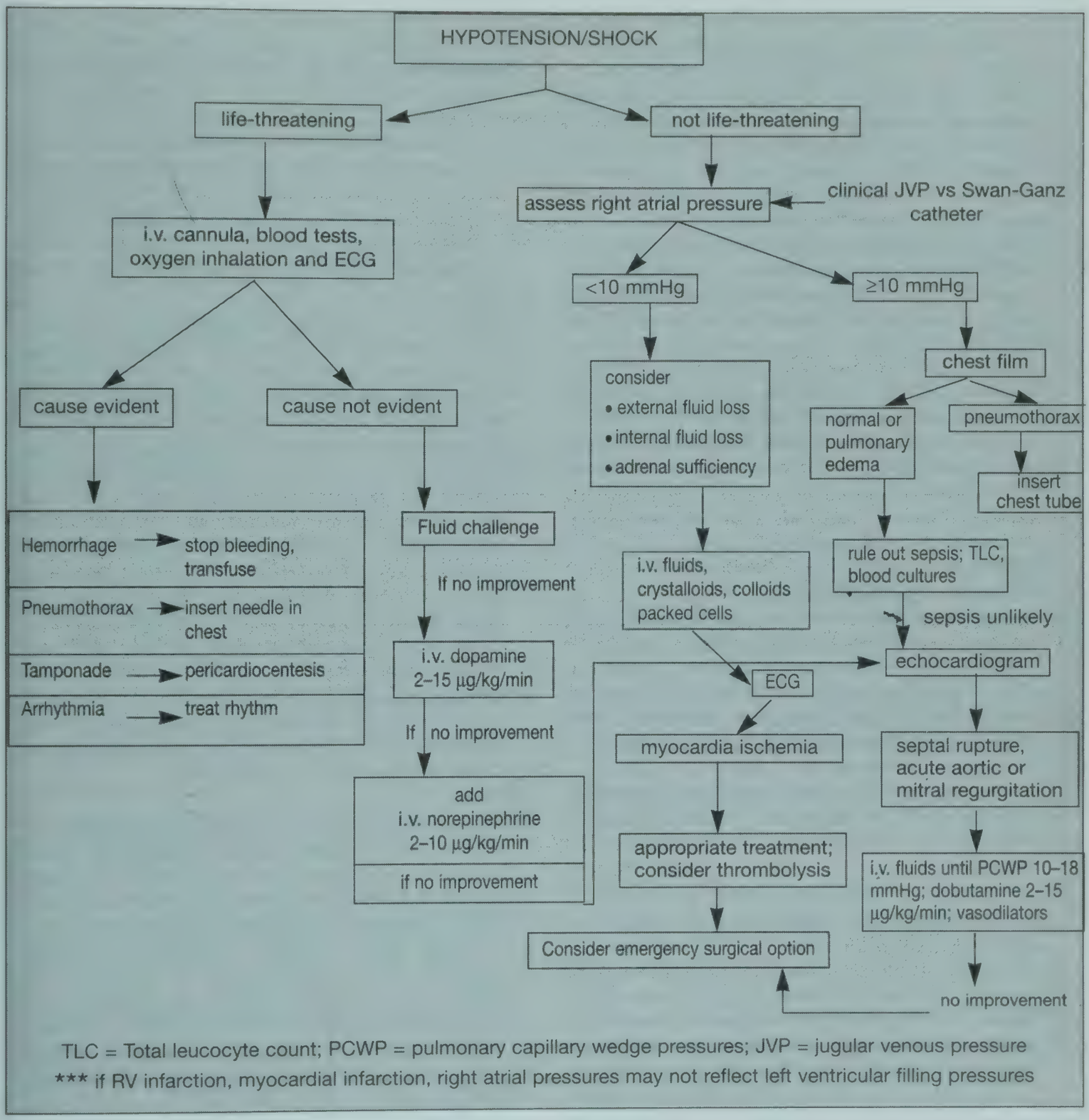


Table 12.9 Algorithm for management of shock

maintain optimal hemodynamics. The management of cardiogenic shock and anaphylaxis are discussed separately in the individual sections.

KEY CONCEPTS

Chest pain

- Chest pain may arise from any of the thoracic structures: the musculoskeletal structures, the heart, pericardium and great vessels, the pleura or the esophagus. Chest pain may be localised (e.g., fractured ribs, Tietze syndrome, herpes zoster) or poorly localised (cardiac, aortic or esophageal pain).
- The pain of angina is a retrosternal feeling of heaviness or constriction (depicted by a fist held against the chest) that is typically provoked by exertion or emotion and is relieved by rest or nitroglycerin; the pain may radiate to the left arm or the jaw, is brief (lasts a few minutes at least but for <15 minutes), and is accompanied by an increase in heart rate-blood pressure product and ECG changes. When pain which is anginal in character is more severe and prolonged, acute myocardial infarction or unstable angina should be suspected.
- Pericardial pain is sharp, has a pleuritic component, often radiates to the trapezius ridge and is relieved by leaning forward. It is usually accompanied by a bi- or triphasic pericardial friction rub.
- The pulmonary causes of chest pain include pleurisy, pneumothorax and pulmonary embolism; usually the clinical picture is suggestive and dyspnea is a frequent clinical accompaniment. Esophageal pain (such as predominant burning character) is provoked by food (hot drinks), recumbency and may be relieved by standing and with antacids.
- The pain of aortic dissection is acute, tearing in quality, may migrate to the interscapular region and may be accompanied by pulse deficits or the murmur of aortic regurgitation.

Edema

- Edema may be generalised or localised. Generalised edema is seen when more than 3 litres of fluid accumulates in the interstitial space. Generalised edema may be due to cardiac, renal or hepatic causes. When edema is related to increased venous pressure, it is pitting in quality. Cardiac edema (usually due to CHF) tends to be more evident on the dependent parts (ankles, sacrum). Edema due to renal disease (nephrotic or nephritic syndromes) may be more evident in the periorbital region in children. Edema related to hepatic dysfunction (cirrhosis with portal hypertension, hepatic failure) is associated with a significant collection in the peritoneal cavity (ascites). A non-pitting edema of legs is seen in hypothyroidism (due to subcutaneous accumulation of mucopolysaccharides).
- Lymphatic edema tends to be non-pitting in quality. It is usually related to acquired lymphatic obstruction or due to a congenital cause (Milroy's disease).
- Localised edema is often due to a local vascular or lymphatic pathology. Venous obstruction or phlebitis is associated with localised edema; edema often responds to elevation of the extremity.
- The treatment of generalised edema depends on the underlying etiology; usually a combination of dietary salt restriction and diuretics is helpful.

Palpitations

- Palpitations are a subjective awareness of the heart beat. When there is a history of a feeling of skipped beats, ventricular extrasystoles are often the underlying cause. When there is a history of sudden onset of an irregular heart beat, atrial fibrillation may be likely.
- If palpitations are sudden in onset and offset, and regular in character, paroxysmal supraventricular tachycardia may be the etiology; often such atrial tachyarrhythmias are associated with polyuria due to an increased production of atrial natriuretic peptide.
- If palpitations are due to the slow forceful beating of the heart, a bradyarrhythmia may be the mechanism. When palpitations are associated with light-headedness or syncope, a reduction in cardiac output is likely and the underlying arrhythmia may be of a serious nature.
- Important investigations include a resting 12-lead ECG and a 24-hour ambulatory Holter recording. Thyroid function tests may be ordered due to an association of thyrotoxicosis with atrial arrhythmias.

Syncope

- Syncope is a brief loss of consciousness, usually the consequence of reduced cerebral perfusion secondary to a decrease in cardiac output. Possible mechanisms include peripheral vasodilatation, a decreased venous return, hypovolemia and cardiac outflow obstruction.
- Common causes include vasodepressor syncope (common faint), arrhythmic (brady- and tachyarrhythmic) syncope, defective baroreceptor function, and metabolic abnormalities (hypoglycemia, hypocapnia).
- Syncope must be differentiated from a seizure. Seizures are often preceded by an aura, are associated with postictal somnolence and the duration of unconsciousness is longer.
- The vasodepressor (vasovagal) syncope is the most common type. It occurs in the upright position and is precipitated by unpleasant physical/emotional stimuli. It is often preceded by vagal symptoms (nausea, vomiting, sweating) and is associated with prompt recovery. Cough syncope and micturition syncope are examples where the syncopal episode is precipitated by a decrease in venous return due to performance of an involuntary Valsalva maneuver.

- Exertional syncope suggests cardiac outflow tract obstruction (aortic or pulmonic stenosis, hypertrophic cardiomyopathy). Postural syncope may be a feature of cardiac myxomas and orthostatic hypotension. Arrhythmic syncope (e.g. Stokes-Adams attacks) have a sudden onset and offset, and may be preceded by palpitations (tachyarrhythmias).
- A detailed history and physical examination yield valuable clues to the etiology of syncope. The physical examination must include evaluation for cardiac murmurs, assessment of blood pressure changes with changes in posture, and if possible, a carotid sinus massage (performed in a monitored setting).
- Important investigations include the resting 12-lead ECG (it may suggest preexcitation, QT prolongation, AV block or ischemia), a 24-hour ambulatory ECG recording (if episodes are frequent), electrophysiologic studies (if syncope is infrequent and an arrhythmic etiology is likely), and a routine blood sugar. A tilt table test may help identify vasodepressor syncope while an echocardiogram may identify ventricular outflow tract obstruction. An EEG may be ordered if a seizure disorder is suspected.
- The treatment depends on the underlying cause: surgical correction of ventricular outflow tract obstruction, pacemaker therapy for bradyarrhythmic syncope, drugs and anti-tachycardia devices for tachyarrhythmic syncope, and elastic stockings for autonomic dysfunction.

Postural hypotension

- Postural hypotension refers to a fall in blood pressure of >20/10 mmHg (systolic/diastolic) on assuming an upright posture.
- The common causes include absolute hypovolemia (diuretic abuse, salt restriction), relative hypovolemia (vasodilator drugs, sepsis), decreased baroreceptor responsiveness (along with decreased arterial compliance, especially in the elderly) and conditions with impairment of autonomic reflexes (*drugs*: m-dopa, clonidine, ganglion-blockers; *neurologic conditions:* peripheral neuropathy due to diabetes, amyloid, alcoholism; Guillain-Barre syndrome; familial dysautonomia; cord lesions like tabes dorsalis, syringomyelia; extrapyramidal syndromes like Parkinson's disease; surgical sympathectomy).
- A detailed history and physical examination often suggest the cause.
- The treatment depends on the cause. Salt and fluid repletion is curative in hypovolemic patients. Propranolol may be substituted for other drugs in hypertensives with postural hypotension. Fludrocortisone and elastic stockings are adjunctive measures that may be used with caution (the former may cause supine hypertension).

Shock

- Shock is a state of circulatory failure which results in inadequate tissue perfusion and which is usually associated with hypotension and oliguria. Shock may be cardiogenic (usually due to a large MI with pump failure), hypovolemic (hemorrhage, GI losses, third space sequestration), vasodilatory (inadequate vasomotor tone as in sepsis) or mechanical (massive pulmonary embolism, tamponade).
- Hypotension associated with shock triggers the release of catecholamines and other hormones (cortisol, ADH, glucagon, renin- angiotensin system) and stimulation of baroreceptors; these factors elevate sympathetic nervous tone with consequent tachycardia, a narrow pulse pressure and other features.
- Shock is generally associated with cold, clammy extremities (skin hypoperfusion and peripheral vasoconstriction), tachycardia, sweating (sympathetic overactivity), oliguria (renal hypoperfusion), restlessness and confusion (cerebral hypoperfusion).
- One exception to this presentation is the initial stage of septic shock; there is fever, extremities are warm (warm shock; peripheral vasodilation), the pulse may be bounding and blood pressure may be maintained.
- Baseline investigations should be obtained and must include renal parameters, electrolytes, glucose and leucocyte count. Blood cultures must be obtained in the febrile patient. Arterial blood gases provide an index of the degree of tissue perfusion (pH) and adequacy of oxygenation. An ECG and chest X-ray must be obtained and urinary output must be monitored.
- General therapeutic measures include resuscitation by ensuring a patent airway and respiratory effort, ensuring a large bore vascular access.
- The management of shock is facilitated by arterial cannulation (intraarterial BP), establishing a central venous line (measure of RA pressure)or inserting a Swan-Ganz catheter (for measuring PCWP); these serve to assess the degree of hypovolemia and can be used to guide fluid therapy.
- Specific treatment depends on the underlying cause. Replacement of blood is important for hemorrhagic shock, while colloids are preferred for the correction of hypovolemic non-hemorrhagic shock. Broad-spectrum antibiotics are indicated in septic shock. Inotropic support (pharmacologic) and IABP have a major role in the management of cardiogenic shock. Pericardiocentesis provides relief in tamponade while thrombolysis is indicated in massive pulmonary embolism with shock.

12.3 Diagnostic methods in cardiology

CHEST RADIOGRAPHY

The chest radiograph is a standard, easily obtained imaging procedure for the subject with suspected cardiac disease. It is often used as an initial tool to screen for cardiac disease by looking at the chamber size, lung parenchyma, pulmonary vasculature and pleural cavities. It is also used for serial follow-up to assess the progression or the resolution of cardiac disease (Fig 12.12).

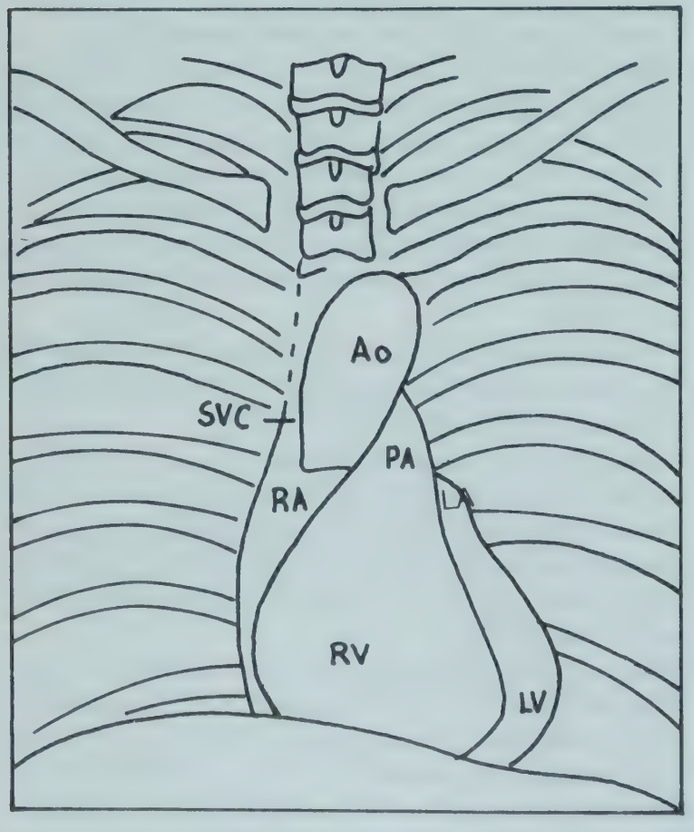


Fig 12.12 Schematic illustration of parts of the cardiac silhouette on the PA chest X-ray.
Ao = aorta, SVC = superior vena cava, RA = right atrium, RV = right ventricle, LA = left atrium, LV = left ventricle, PA = pulmonary artery

The right border of the cardiac silhouette on the frontal chest radiograph is made up of the superior vena cava above, and the right atrium below. Still further inferiorly, the inferior vena cava can be seen as a triangular shadow between the right atrium and the diaphragm. The left heart border is formed (from above downwards) by the aortic knob, the main pulmonary artery, a concavity called the *pulmonary bay* (where a small portion of the left atrial appendage lies) and the anterolateral and apical portions of the left ventricle. In the lateral chest film, the anterior part of the cardiac silhouette is composed of the ascending aorta followed inferiorly by the right ventricle that lies in the retrosternal space separated from the sternum by interposed lung tissue. The posterior part of the cardiac silhouette is formed by the posterior portion of the left atrium above and by the posterior wall of the left ventricle inferiorly.

The overall size of the heart on the chest radiograph is determined using the *cardiothoracic ratio.* To measure the cardiothoracic ratio, a midline is drawn through the spinous processes of the vertebrae. The greatest perpendicular distances from this line to the right and left cardiac borders are obtained and added. This sum is divided by the maximum transverse thoracic measurement to yield the cardiothoracic ratio. A cardiothoracic ratio greater than 0.5 is considered abnormal. It must be remembered that the heart size as

measured on a chest film is a gross estimate and is affected by several factors such as the position of the patient (supine films have a larger cardiac silhouette), the degree of inspiration (heart size seems to be larger in an expiratory film), the presence or absence of chest deformities, ascites or emphysema.

Dilatation of the right atrium enlarges the right border of the cardiac shadow. The left atrium, however, tends to dilate posteriorly and its enlargement appears as an increased density of the cardiac silhouette behind the right atrial shadow *(double density sign).* Left atrial enlargement also elevates the left main stem bronchus thereby increasing the normal carinal angle from 80–90° to an obtuse angle. In rheumatic valvular heart disease left atrial enlargement invariably enlarges the appendage and this appears as a convexity (that is, a relative straightening) of the left heart border below the main pulmonary artery segment.

When the left ventricle enlarges, the cardiac apex on the frontal radiograph is displaced downwards and to the left. This typically occurs in the volume-loaded left ventricle (as in valvular regurgitation or dilated cardiomyopathy). In conditions of left ventricular pressure overload, as in hypertension or aortic stenosis, the ventricle undergoes concentric hypertrophy and the cardiac silhouette may appear normal. Right ventricular enlargement is difficult to discern on the frontal chest radiograph as the right ventricle is not border-forming. However, the cardiac apex may be displaced upwards and to the left. The right ventricle dilates anteriorly and therefore, a lateral chest film will detect its enlargement better; it is evidenced as a decrease in the retrosternal translucency.

The pulmonary vasculature is also evaluated from the chest radiograph. The normal chest X-ray may reveal the presence of upto three end-on vessels at the hilum. When there is an underlying shunt lesion with an increased pulmonary arterial flow (*pulmonary plethora*) these end-on vessels become numerous. As pulmonary vascular resistance rises and shunt flow diminishes, the main pulmonary artery dilates and the peripheral vasculature appears attenuated: this is termed *peripheral pruning*. An enlarged central pulmonary artery shadow with a right lower lobe pulmonary artery size of more than 16 mm in the absence of increased vasculature in the lung fields suggests primary pulmonary hypertension as the likely etiology of these findings. A paucity of vessels on the chest film is termed *oligemia* and may suggest a significant right to left shunt such as in tetralogy of Fallot. Pulmonary venous hypertension appears as a prominence of upper lobe pulmonary veins, initially becoming equal to the normally more prominent lower lobe veins (*equalisation*), followed later by a greater relative prominence of the former as compared to the latter (*cephalisation* or *antler sign*). Interstitial pulmonary edema takes the appearance of *Kerley B lines* which reflect engorged subpleural lymphatics. Alveolar pulmonary edema causes confluent bihilar infiltrates and produces a hilar *butterfly sign.*

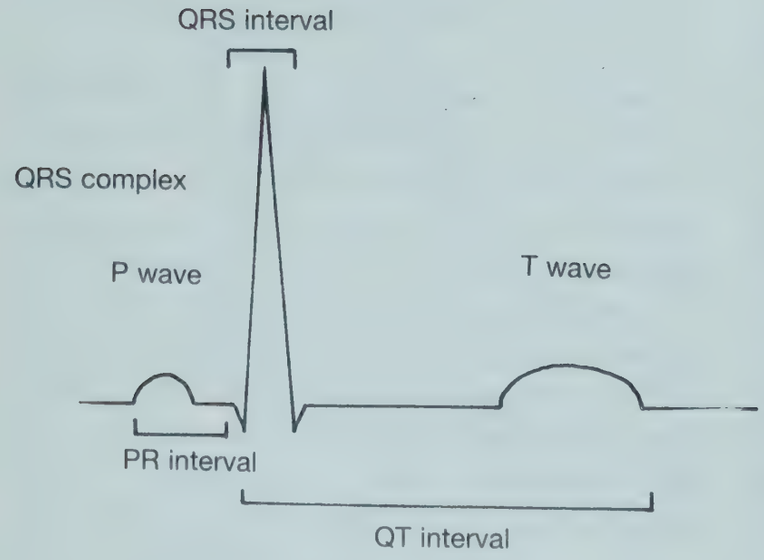
Specific radiographic signs of individual cardiac diseases are discussed under these respective sections.

ELECTROCARDIOGRAPHY

The normal electrical activity of the heart can be recorded simply by placing metal electrodes on the skin as the human body acts as a volume conductor and the surface electrical activity reflects the intracardiac electrical activities. The ECG or EKG (*electrocardiogram*) reflects the summation of the action potentials of all cardiac cells. The normal initial low amplitude and low frequency deflection of the ECG is the P wave which represents *atrial depolarisation.* This is followed by a rapid high amplitude deflection, the QRS complex which reflects *ventricular depolarisation,* that is phase 0 of the cardiac action potential. The portion of the ECG

between the P wave and the QRS complex is called the PR segment and is isoelectric, that is, neither positive nor negative. The interval from the beginning of the P wave to the beginning of the QRS complex is the PR interval. This interval is a measure of the time necessary for an electrical impulse originating in the sinoatrial node to travel through the atrium, AV node, and His-Purkinje system (upto the point where the impulse activates the ventricular myocardial cells). The normal PR interval varies between 0.12 and 0.20 seconds in duration. A PR interval greater than 0.20 seconds is called a first degree AV (atrioventricular) block. The initial negative deflection of the QRS complex is called the Q wave; the initial positive deflection is termed the R' wave; and if a subsequent negative deflection is present, it is called the S wave. Any positive deflection after the S wave is termed the R' wave.

The duration between the onset of and the termination of the QRS complex is called the QRS interval and is normally less than 0.10 seconds. The interval from the onset of Q wave to the downward deflection of R wave is termed the *intrinsicoid deflection time* and varies normally from 0.03–0.05 seconds. Upper and lower case letters are used to indicate the relative size of the QRS components; thus QRs indicates a large Q and R waves and a small S wave. The QRS complex is followed by a low-amplitude low-frequency deflection termed the T wave, which represents ventricular repolarisation (phase 3 of the action potential). The isoelectric portion of the ECG between the QRS complex and the T wave is the ST segment (phase 2 of the action potential). The junction of the QRS complex and the ST segment is termed the *J point*. The interval from the beginning of the QRS complex to the end of the T wave is the QT interval represents the time for ventricular electrical systole. This interval is a measure of ventricular refractoriness and decreases with an increase in heart rate. The normal QT interval varies from 0.35–0.44 sec in duration for heart rates between 60–100 beats per minute. The *Bazett formula* corrects the QT interval for heart rate and yields a heart rate-corrected interval,



Normal electrocardiographic values

P wave	Duration <0.11 sec, amplitude <2.5 mm in lead II
PR interval	0.12–0.2 sec
QRS	Duration <0.12 sec
complex	Amplitude : R wave in V6 (RV6) < 25 mm RV6+SV1 <35 mm Axis-30°—90°
Q wave	Duration <0.04 sec Amplitude <25% of total QRS complex amplitude
QT interval	0.38–0.42 sec (corrected for heart rate)
ST segment	should be isolelectric
T wave	May be inverted in III, aVR, V1 and V2

Fig 12.13 Diagram of a normal ECG cardiac cycle in normal sinus rhythm. The P wave and T wave are both demonstrated, along with the PR, QRS and QT intervals

$QT_C = QT/\sqrt{R–R}$ interval.

The QT_C interval is normally less than 0.42 sec in men and 0.43 sec in women. Occasionally the T wave is followed by a broad, low-amplitude deflection termed a U wave.

The ECG is recorded on special paper that is run at a speed of 25 mm/sec by convention. The paper is divided into grid-like boxes, each small box being 1 mm in size. Each millimeter horizontally represents 0.04 seconds and vertically represents 0.1 mV. At 5 mm intervals, heavier horizontal and vertical lines are drawn on the paper. The electrodes are connected to the left arm, the left leg and the right arm, with the right leg being grounded. Twelve leads are recorded on the standard ECG—these include six frontal plane leads and six precordial leads. The six extremity leads record voltages from the heart directed onto the frontal plane (which divides the body into front and back halves). These include three unipolar leads (aV_R, aV_L, and aV_F) and three bipolar leads I, II and III. A bipolar lead records the difference between voltages from the heart detected at the two extremities. Thus, lead I displays the electrical potential difference between the left and right arms (the left arm being the positive terminal); lead II, the difference between the right arm and the left leg (the left leg being positive) and lead III the potential difference between the left arm and the left leg (the left leg being positive). The bipolar extremity leads are represented by *Einthoven's triangle* (Fig 12.14) and are related by the mathematical expression II = I + III. The unipolar extremity leads record voltages at one point relative to a central point at zero potential. These are related by the equation:

$aV_R + aV_L + aV_F = 0$.

When taken together the six extremity leads describe a full circle in the frontal plane at 30° intervals–the hexaxial reference system (Fig 12.15).

The six precordial (chest) leads record voltages from the heart directed onto the horizontal plane of the body that divides the

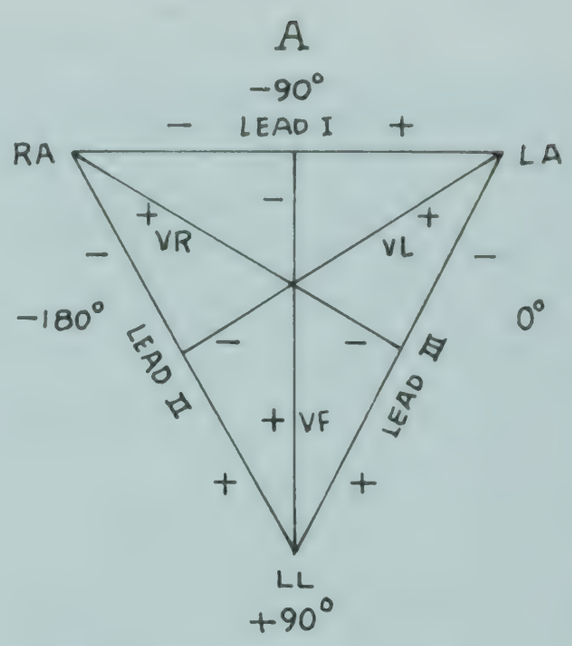


Fig 12.14 Einthoven's triangle

body into an upper and a lower half. They are termed V_1 to V_6 and are taken with the electrodes in specific anatomic positions (Fig 12.16). The appearance of the deflections in a particular lead is governed by a very basic law; a positive (upward) deflection will be seen in any lead if electrical depolarisation spreads towards the positive pole of that lead; a negative (downward) deflection is seen if depolarisation spreads towards the negative pole of the lead; and an isoelectric or biphasic deflection is seen when the depolarisation starts in the sinoatrial node and spreads downwards to the subject's left (towards the positive pole of lead II and away from the positive pole of aV_R). The P wave will always be positive in lead II and negative in lead aV_R. Ventricular depolarisation is more complex and consists of an initial phase wherein the ventricular septum is depolarised from the left to the right (towards lead V_1 and away from lead V_6). This produces a small q wave called the septal q wave in lead V_6 and a small r wave called the septal r wave in lead V_1. This is followed by another phase of depolarisation when the stimulus spreads through the right and left ventricles. Since the mass of the left ventricular myocardium exceeds that of the right ventricle, the nett direction is towards the left

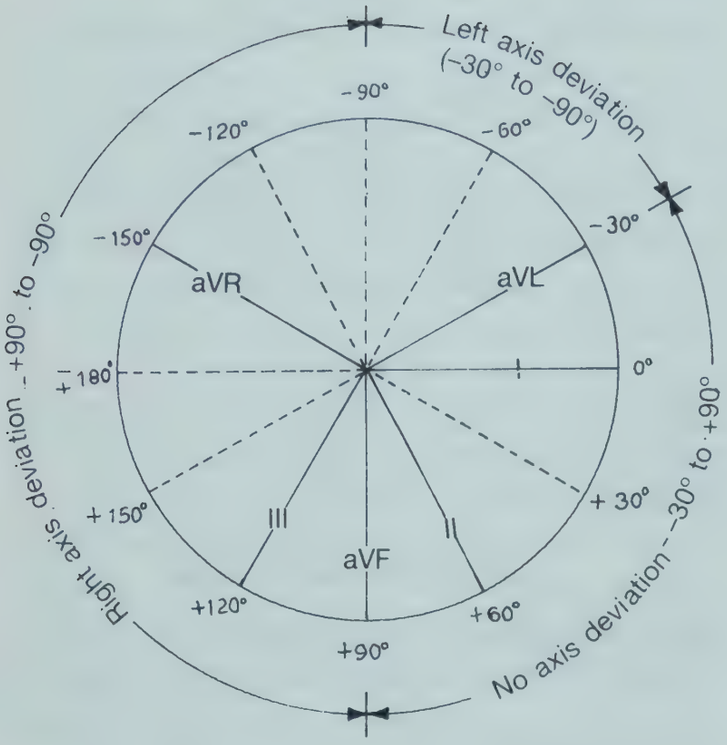


Fig 12.15 Hexaxial reference figure for frontal plane axis determination, indicating values for abnormal left and right QRS axis deviation

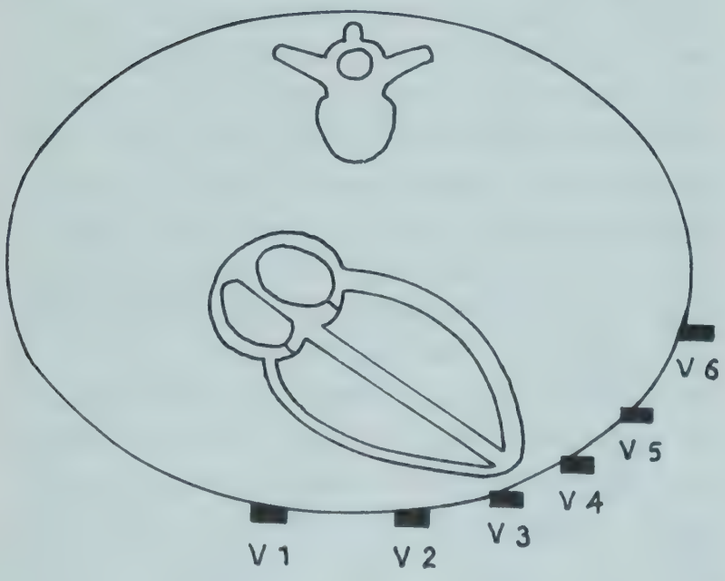


Fig 12.16 Diagram of orientation of precordial ECG leads. Leads V_1 and V_2 overlie the right ventricle leads V_3 and V_4 are transitional leads between the right and left ventricles, and leads V_5 and V_6 overlie the left ventricle

chest leads. This produces a tall R wave in leads V_5 and V_6 and a deep S wave in leads V_1 and V_2. Chest leads between these two positions show a *transitional pattern* with tall R waves and deep S waves. If the right precordial leads (V_1, V_2) have relatively equal R and S waves with no other abnormality, counterclockwise rotation is said to be present. If the left precordial leads (V_5, V_6) have equal R and S waves, clockwise rotation is said to be present. In the extremity leads the QRS complex varies depending on whether the heart is more horizontal or vertical. When the heart is vertical, leads II, III, and aV_F show a qR pattern; when the heart is horizontal, the leads I and aV_L show a qR pattern.

The normal T wave generally follows the direction of the QRS complex deflection. In the chest leads the T wave is positive in the left-sided leads and generally positive in lead V_2 as well. The T wave in lead V_1 may be negative or positive.

The term *mean QRS axis* describes the direction of the QRS vector in the hexaxial frontal plane of the body. The mean QRS vector is determined as being midway between the two leads with the greatest R waves or as being at right angles to the lead with biphasic QRS complexes. The normal QRS axis lies between +100° and –30°. An electrical QRS axis more positive than +100° is referred to as *right axis deviation* and is generally seen as tall R waves in lead III and deep S waves in lead I. The causes of right axis deviation include right ventricular hypertrophy, chronic lung disease, left posterior hemiblock, and lateral wall myocardial infarction. When the QRS axis is more negative than –30°, *left axis deviation* is said to be present. This manifests as tall R waves in lead I and deep S waves in lead III. The causes of left axis deviation include left ventricular hypertrophy, left anterior hemiblock and congenital heart defects like a common atrioventricular septal defect or an atrial septal defect of the primum type. Occasionally the QRS axis lies between –90° and –180°; this is referred to as an *indeterminate* or *northwest axis*.

Table 12.10 ECG criteria for chamber hypertrophy/enlargement

Criteria for left atrial enlargement (Fig 12.17)	Criteria for right atrial enlargement (Fig 12.18)
• P wave duration ≥0.12 sec • notched, slurred P waves in lead I & II (distance between notches ≥0.03 sec) - *P mitrale*. • biphasic P waves in V_1 with a wide, deep, negative terminal component • mean P wave axis shifted to left (from +45° to –30°).	• tall peaked P waves ≥2.5 mm in amplitude in II, III, AVF (P pulmonale) • P wave duration < 0.11 sec • mean P wave axis shifted to right (≥ +70°)

Criteria for left ventricular hypertrophy (Fig 12.19)		Criteria for right ventricular hypertrophy (Fig 12.20)	
Voltage criteria		*Voltage criteria*	
$R_I + S_{III}$	≥ 2.5 mV	R in V_1	≥ 0.5 mV
R in AV_L	> 1.2 mV	R/S in V_1	> 1
R in AV_F	> 2.0 mV		
S in V_1	> 2.4 mV		
R in V_5/V_6	> 2.6 mV		
$R_{V5/V6} + S_{V1/V2}$	> 3.5 mV		
Others		*Others*	
Strain pattern (ST depression with T wave inversion V_5/V_6)		strain pattern (V_1 or V_2)	
Delay in intrinsicoid deflection in V_5/V_6 ≥0.05 sec		Delay in intrinsicoid deflection in V_1/V_2 ≥0.03 sec	

The ECG can be used to diagnose chamber enlargement and hypertrophy (Table 12.10). It can be used to diagnose conduction blocks in the right bundle or either (or both) components of the left bundle (Table 12.11). The term *bifascicular block* refers to either a complete left bundle branch block or to the combination of complete right bundle branch block with left anterior or posterior hemiblock. Other types of conduction disturbances are described in Chapter 12.7.

The ECG is very useful in the evaluation of subjects with ischemic heart disease. Classically, ischemic ECG changes have been classified into three groups. ST segment depression has been thought to represent *ischemia*, ST segment elevation has been thought to represent myocardial *injury* and abnormal Q waves have been associated with myocardial *necrosis*. However, a close correlation between these ECG features and specific pathologic abnormalities has not been found. Though Q waves roughly correlate with transmural necrosis, they have also been seen with subendocardial necrosis. Similarly, ST segment abnormalities have been associated with both subendocardial and transmural necrosis. For these reasons, the pathologic terms subendocardial and transmural infarction have been replaced with the terms Q wave or Non-Q wave infarction. A pathologic Q wave is one which is more than 0.04 seconds in duration and is more than 25 per cent of the height of the R wave in the same lead. *Pathologic* Q waves are seen in the absence of infarctions

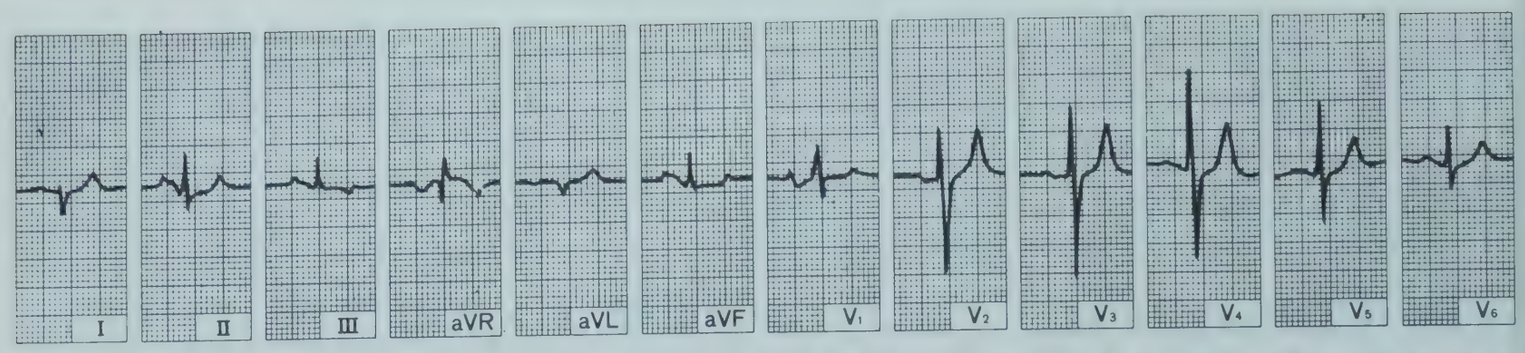


Fig 12.17 Left atrial hypertrrophy (MS): wide notched P in II, III, aVF, V_{4-6}; diphasic P in V_1 with broad negative phase ('mitral' P waves)

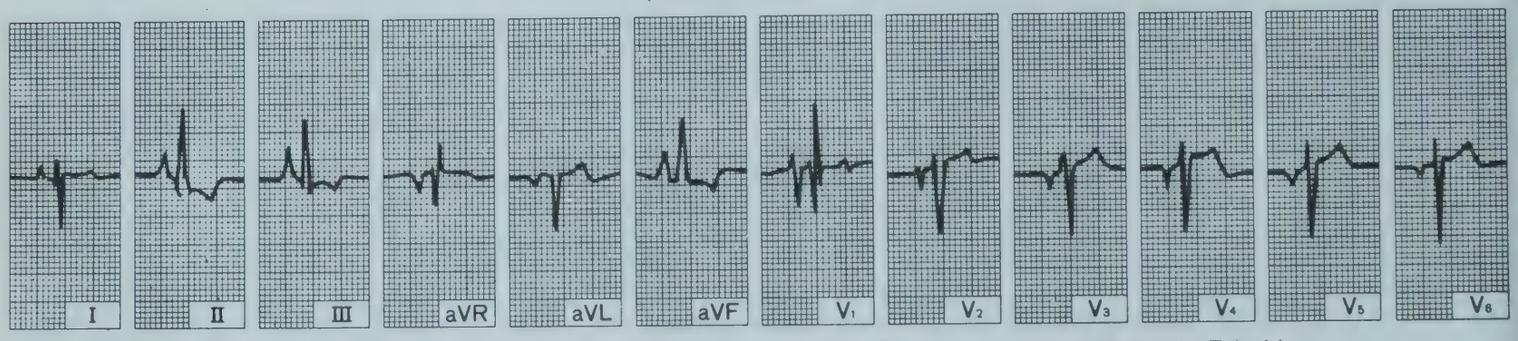


Fig 12.18 Right atrial hypertrophy (CPD): tall, peaked P in II, III; large diphasic P in V_1

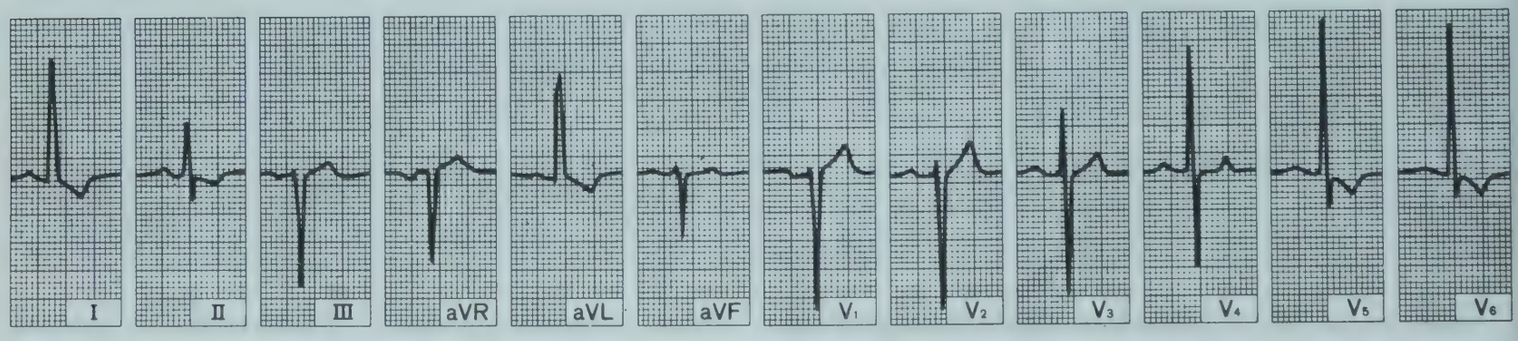


Fig 12.19 Left ventricular hypertrophy (hypertensive cardiovascular disease: left axis deviation, tall R in aVL, depressed ST segment in V_{5-6}, inverted T in I and aVL, inverted T in V_{5-6}

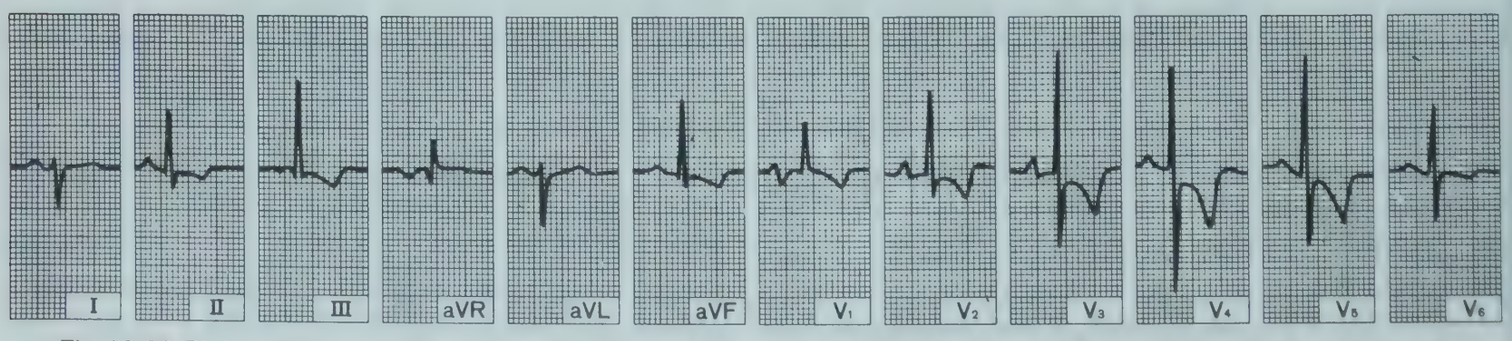


Fig 12.20 Right ventricular hypertrophy (MS): large R in wave in V_1, amplitude of R wave decreases as S waves increase from V_5 to V_6, inverted T in V_{1-6}, depressed ST segment in V_{2-5}, lead aVF resembles, V_1, right axis deviation

in other conditions such as hypertrophic cardiomyopathy, dilated cardiomyopathy, left ventricular hypertrophy, pulmonary embolism, chronic lung disease and the Wolff-Parkinson-White syndrome. The sequence of ECG changes seen in acute Q wave

Table 12.11 ECG criteria for bundle branch blocks and fascicular blocks

(A) Criteria for complete left bundle branch block (LBBB) (Fig 12.21)	(B) Criteria for complete right bundle branch block (RBBB) (Fig 12.22)
• QRS duration ≥0.12 sec • broad, slurred or notched R waves without a preceding q wave in V_6 • deep wide QS (occasionally an rS with a wide S wave) in V_1 • Secondary ST-T wave changes • Late intrinsicoid deflection (≥0.05 sec) in V_5/V_6	• QRS duration ≥0.12 sec • rSR' with a prominent wide final R' in V_1 • deep terminal slurred S wave in V_5, V_6 with normal septal q waves • inverted T waves in V • late intrinsicoid deflection (≥0.03 sec) in V_1
(C) Criteria for incomplete LBBB	**(D) Criteria for incomplete RBBB**
• QRS duration 0.10–0.12 sec; rest as (A)	• QRS duration 0.10–0.12 sec; rest as (B)
(E) Criteria for left anterior fascicular block (left anterior hemiblock)	**(F) Criteria for left posterior fascicular block (left posterior hemiblock)**
• QRS ≤0.10 sec • left axis deviation (–45° or greater) • qR in leads I and AV_L • rS pattern in leads II, III and AV_F.	• QRS ≤0.10 sec • right axis deviation (+90° or greater) • rS in leads I and AV_L • qR in leads II, III and AV_F. • Exclude other causes of right axis deviation (right venticular hypertrophy, lateral wall myocardial infarction, chronic lung disease)

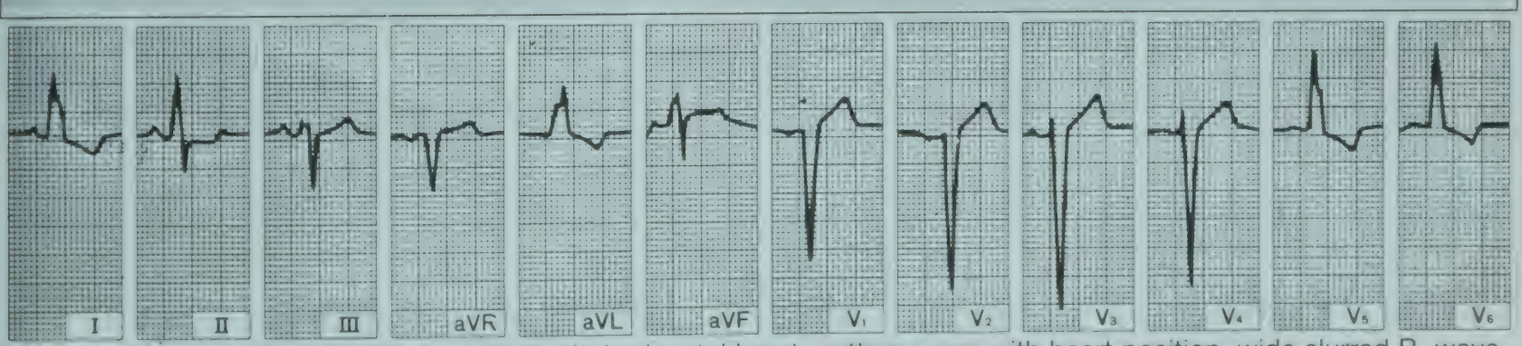


Fig 12.21 Complete left bundle branch block: horizontal heart, patterns vary with heart position, wide slurred R wave in 5–6, QRS interval 0.12 sec, VAT or intrinsicoid deflection prolonged and aVL similar to V_{5-6}, lead I similar to aVL and V_{5-6} with depressed ST segment and inverted T waves.

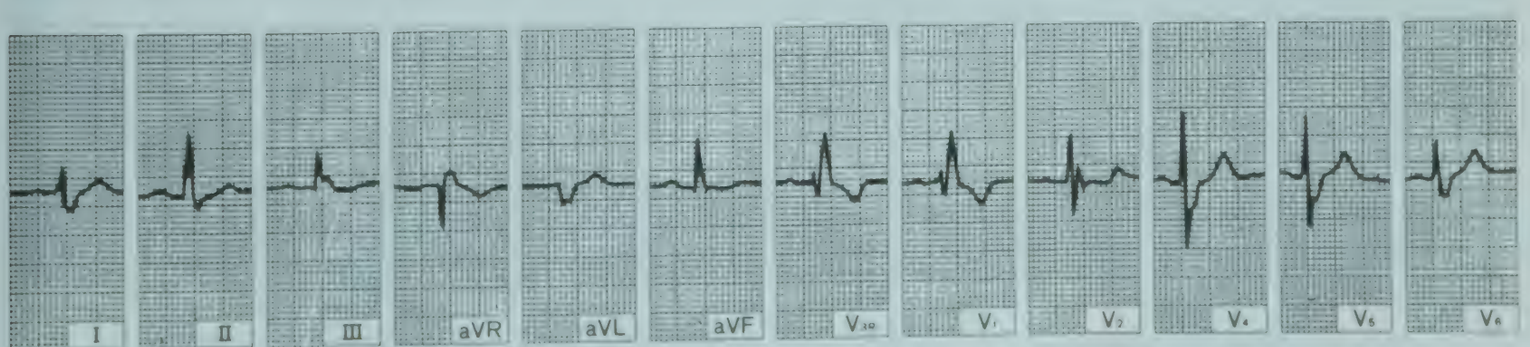


Fig 12.22 Complete right bundle branch block: QRS 0.12 sec or greater, wide slurred S waves in V_{5-6}, rsR' complexes in V_{3R}, V_1 and V_2 with absent Q waves, VAT prolonged in V_{3R}, V_1 and V_2, wide S wave in lead I

myocardial infarction are shown in Fig 12.25 and the ECG-based localisation of infarcts is shown in Table 12.12.

ST segment depression can be seen in reversible ischemia, subendocardial necrosis, left ventricular hypertrophy and with the administration of drugs such as digitalis. Similarly, though traditionally associated with acute infarction, ST segment elevation can be seen in coronary artery spasm (Prinzmetal's angina), left ventricular aneurysm, acute pericarditis, and as part of early repolarisation changes that are variants of the normal.

The ECG can be affected by several disease processes and other factors. Many drugs produce changes in the ECG. The effect of digitalis shows a downsloping ST segment depression (like an inverted tick mark) and is seen in subjects on therapeutic doses of digoxin. Quinidine, procainamide, and diisopyramide can all produce prolongation of the QT interval and can predispose to a potentially lethal type of polymorphic ventricular tachycardia known as *torsade des pointes*. Dyselectrolytemia is a common cause of an abnormal ECG. Hyperkalemia (Fig 12.23) produces an initial narrowing and tenting (peaking) of the T waves with mild elevation of serum potassium levels, which eventually lead to PR prolongation, loss of P waves, widening of the QRS complexes culminating in ventricular fibrillation and asystole if not treated promptly. Hypokalemia (Fig 12.24) can produce ST depression and lead to the appearance of prominent U waves; it predisposes to digitalis-induced arrhythmia. Hypercalcemia shortens the QT interval while hypocalcemia prolongs it.

Acute pulmonary embolism can produce several patterns of abnormalities: 1) right axis deviation, 2) P pulmonale, and 3) $S_1Q_3T_3$ pattern.

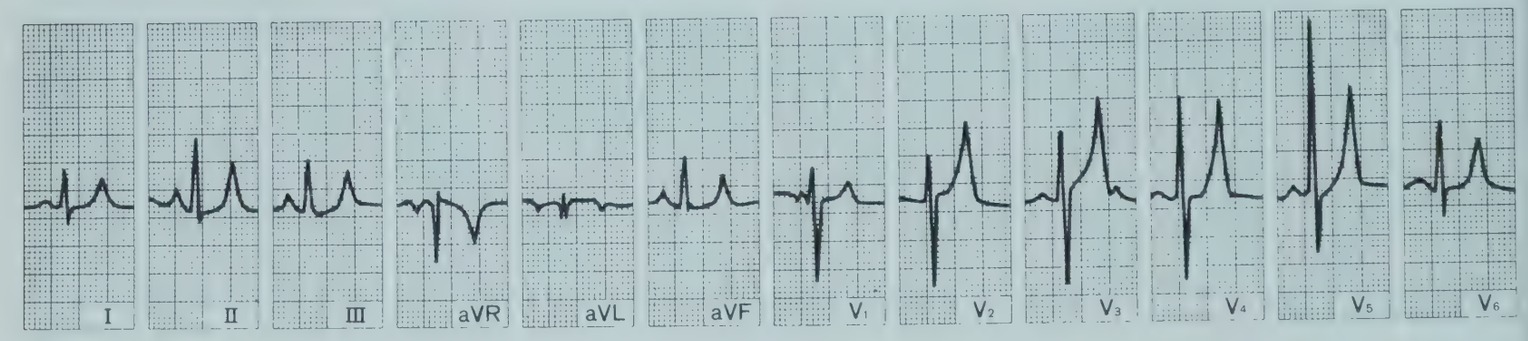


Fig 12.23 Hyperkalemia: tall, peaked T waves are the earliest change, T wave amplitude is usually greatest in precordial leads, atrial standstill may develop as serum potassium increases

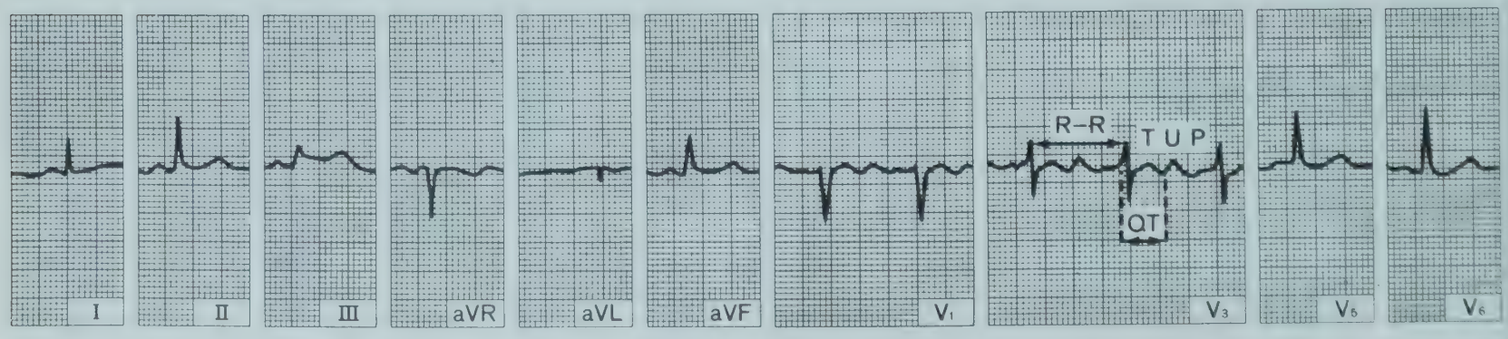


Fig 12.24 Hypokalemia: increased P–R interval commonly seen is not present on this tracing, depression of ST segments in precordial leads is usual, T waves may become depressed, and prominent U waves are noted, QT appears prolonged in some leads where separation from U wave is not distinct

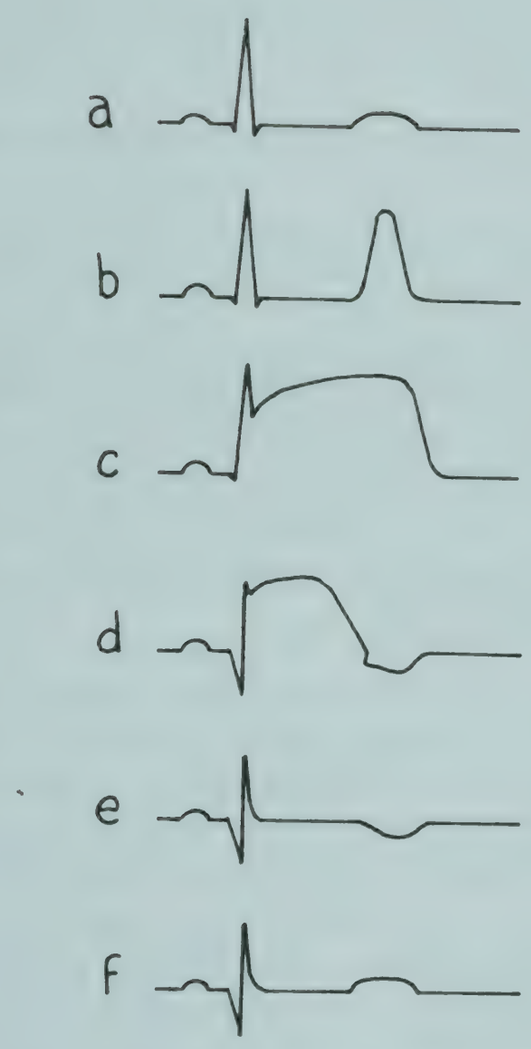


Fig 12.25 The usual sequence of ECG changes seen following acute Q wave myocardial infarction: a) shows a normal QRS complex and ST segment; b) the T wave is tall and symmetrically peaked. This is usually the first ECG change seen in acute infarction, and the T waves are sometimes termed *hyperacute T wave* changes; c) shows ST segment elevation that usually follows within the first hour of acute infarction; d) shows Q waves developing within the first 24 hours, along with T wave inversion; ST elevation persists; e) shows persistence of Q waves and T wave inversion, however, the ST segment elevation has resolved. This usually occurs during the first few days following infarction. After several months, the T wave inversion normalises and the Q waves persist as a permanent marker of prior infarction (f).

Table 12.12 Localisation of myocardial infarction

Area of infarction	*ECG changes*	
Inferior	II, III, aV_F	Q waves ST elevation T wave inversions
Anteroseptal	V_1-V_3	
Anterior	V_3-V_4	
Anterolateral	V_4-V_6	
Extensive anterior	V_1-V_6, I, aV_L	
High lateral	I, aV_L	
Posterior	V_1-V_2 tall broad initial R wave, ST depression, tall upright T wave; usually occurs in association with inferior or lateral MI	
Right ventricular	V_1 and V_{4r}, ST elevation; usually occurs in association with inferior MI	

Acute pericarditis (Fig 12.26) is associated with diffuse ST segment elevations in several leads with PR segment elevation in lead aV_R and depression in the others (related to atrial currents of injury). A pericardial effusion produces low voltage complexes (QRS voltage <5 mm in extremity leads). A massive effusion with tamponade can result in *electrical alternans,* characterised by a beat-to-beat shift in the QRS axis as the heart 'swings' in the effusion (Fig 12.27).

A wide QRS pattern should arouse suspicion of the possibility of a bundle branch block, hyperkalemia, preexcitation (see section 12.7) or a pacemaker rhythm.

EXERCISE STRESS TESTING

The exercise stress test is an objective test of cardiac performance and is used extensively for both diagnostic and prognostic purposes. It is most often used for the evaluation of a subject with chest pain for assistance in the diagnosis (subjects with atypical chest pain), or for prognostication (in case of chronic stable angina pectoris or post-myocardial infarction). It is also used for evaluating a subject with dyspnea of obscure origin and to evaluate the functional

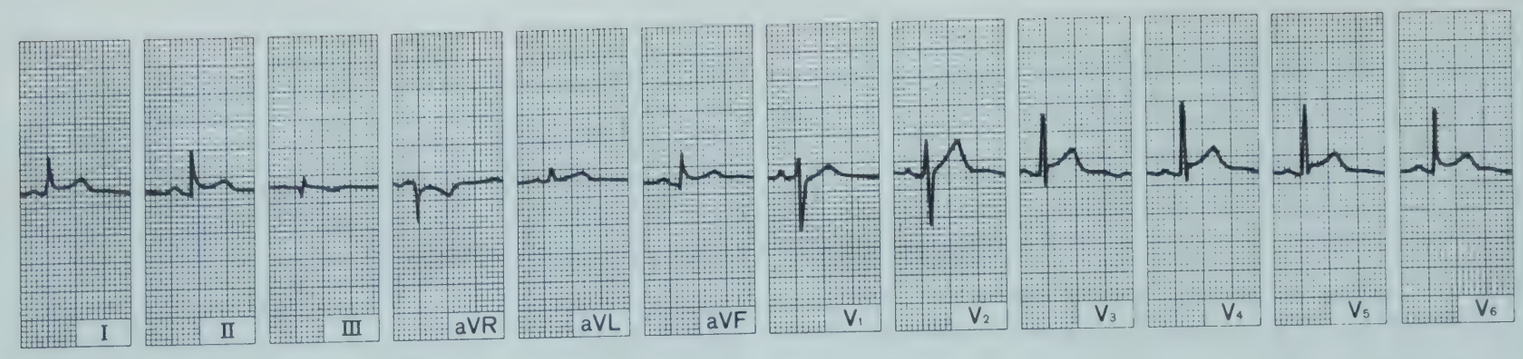


Fig 12.26 Pericarditis: ST segment elevation in I, II, aVL, aVF, V_{2-6}; ST segment changes usually occur in leads overlying the area of pericardial inflammation

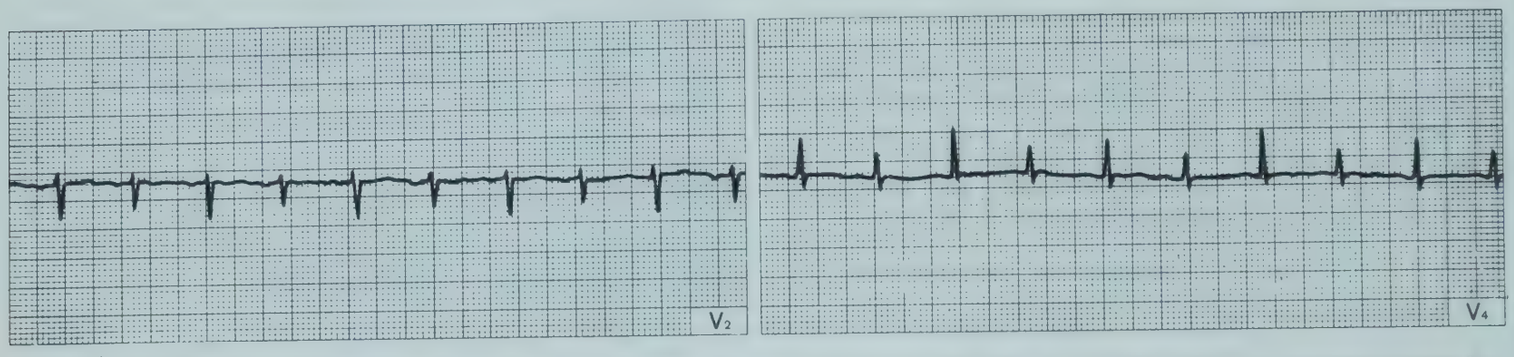


Fig 12.27 Electrical alternans: the height of the R-wave alternately varies, that is, its amplitude in successive beats is different, but similar for every other beat

significance of a 'borderline' coronary artery narrowing.

During exercise, the cardiac output increases five- to sixfold and this is achieved principally by an increase in the heart rate to two to three times its resting value. The systolic blood pressure rises due to increased cardiac output whereas the diastolic pressure stays the same or falls slightly (peripheral vasodilation). The stress of exercise increases the heart-rate–blood-pressure product, which is the critical determinant of myocardial oxygen consumption. In subjects with obstructive coronary artery disease, the coronary blood flow reserve fails to match the increased demand and the myocardium is rendered ischemic. This myocardial ischemia may manifest as chest pain and as ECG changes during the exercise test.

The most common form of exercise is performed on a treadmill. The workload on the treadmill is best expressed in terms of oxygen consumption units or METS (metabolic equivalents). The normal basal myocardial oxygen consumption is 3.5 ml oxygen/kg/minute and is called 1 MET. An exercise level that requires oxygen consumption five times the basal level would therefore be called 5 METS. The intensity of exercise is varied on a treadmill by varying its incline and the speed of the motor. Usually the workload administered is a standardised one which follows a set protocol, for instance the Bruce protocol. Each step-wise increase in speed and treadmill elevation represents an increase in the myocardial oxygen consumption and cardiac work, and is termed a *stage* of the exercise test. The gradual increase in exercise intensity allows a warm-up prior to each stage. A multilead ECG is monitored throughout and the heart rate and blood pressure are recorded every minute. During normal exercise, the heart rate increases with increasing work load till a maximal heart rate is achieved. This maximal heart rate is predicted based on the age and sex of the individual, being lower in females and with old age. Maximal exercise testing generally requires attainment of at least 90 per cent of the predicted heart rate. A submaximal testing protocol (usually requiring

attainment of 70 per cent of the age-predicted heart rate) is used in the period immediately after a myocardial infarction. The exercise test is, however, prematurely terminated before achieving the desired level if the subjects manifest significant symptoms, ECG changes, arrhythmias, or abnormal blood pressure responses (such as a fall in systolic pressure of more than 10 mm below the basal reading or a rise to more than 200 mmHg).

The conventionally accepted ECG criterion of exercise-induced ischemia is the production of ≥1 mm depression of the ST segment measured at 0.08 seconds after the J point, provided the configuration of the ST segment is horizontal or downsloping (Fig 12.28). This is a 'compromise' value to maximise both the sensitivity and the specificity of the test. ECG changes which occur at an early stage of exercise at a low work load, are seen in multiple leads, and take long to recover after stopping the exercise, are predictive of multivessel coronary artery disease. Reversible ST segment elevation can occur with exercise and may be due to severe transmural ischemia (as is seen in disease involving the left main coronary artery) or due to the presence of a ventricular aneurysm. False-positive ECG responses can be seen in the presence of left ventricular hypertrophy, left bundle branch block, mitral valve prolapse, digitalis intake or in preexcitation syndromes.

The exercise test should be performed by experienced physicians and equipment required for cardiac resuscitation should be immediately accessible. The treadmill test should not be performed if it is suspected that the subject has unstable angina or acute myocardial infarction. The complications likely during an exercise test include death (1 in 10,000), cardiac arrest or myocardial infarction (2 to 3 per 10,000).

Ambulatory ECG Monitoring (Holter Recording)

Holter monitoring is used to detect rhythm disturbances in patients with symptoms suggestive of arrhythmias, or to evaluate the efficacy of therapy for arrhythmias. Two surface electrocardiographic leads are usually recorded for a period of 24 hours on a magnetic tape using a recorder secured to the patient's belt. The patient is provided with a diary to record any symptoms. The tapes are scanned with a high

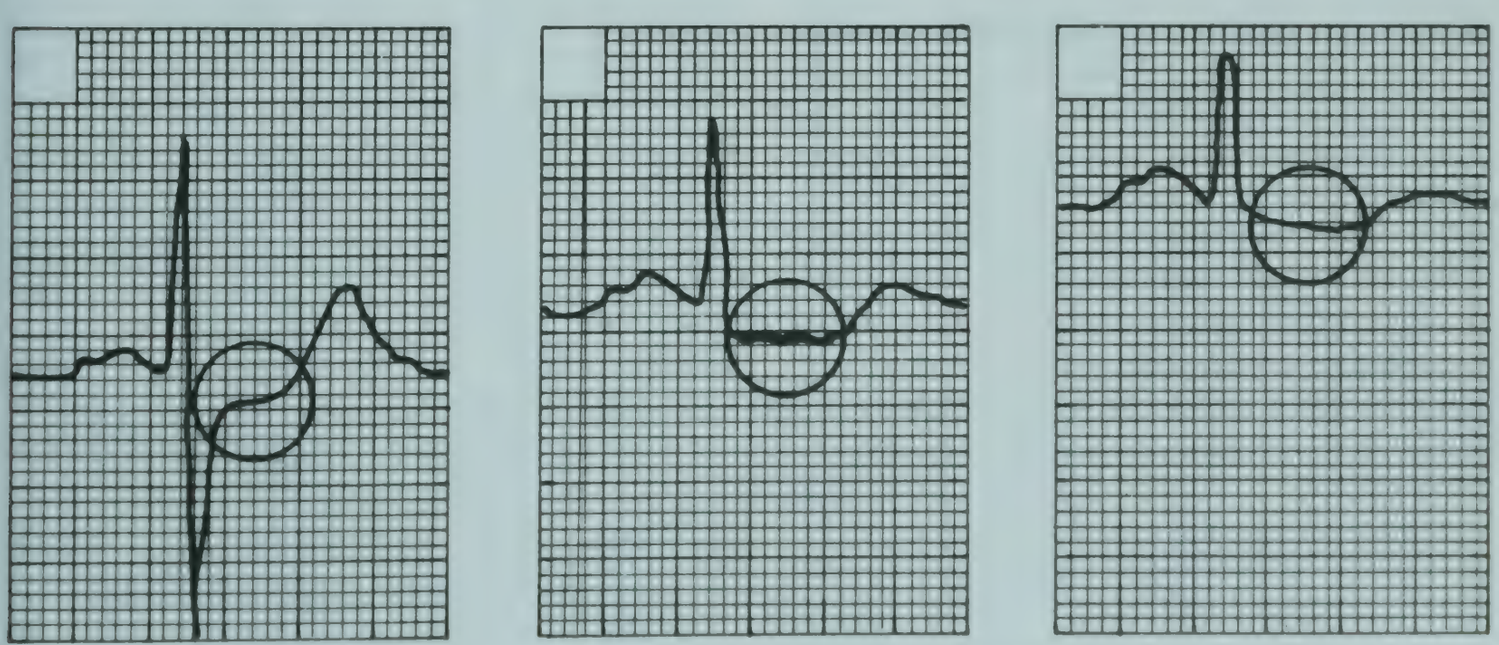


Fig 12.28 ECG criteria

speed analyser and suspicious portions of the record can be printed on ECG paper for the physician's interpretation. It is also used for monitoring the ST segment for evidence of myocardial ischemia.

NUCLEAR CARDIOLOGY

The four principal techniques in nuclear cardiac imaging include: 1) radionuclide angiography, 2) perfusion scintigraphy, 3) infarct-avid scintigraphy, and 4) antimyosin scintigraphy.

To perform nuclear imaging, small doses of radioactive tracers are injected intravenously. The tracer in the intravascular space serves as the imaging agent by emitting gamma ray photons which are detected by a gamma camera positioned over the thorax. For *equilibrium radionuclide angiocardiography* (ERNA), Technetium^{99m} is injected intravenously to label the subject's red blood cells. The cardiac cycle is usually divided into several time intervals or '*gates*' and photon events are summed for several hundred cardiac cycles. The photons imaged produce an image of the heart at each time interval (gate) of the cardiac cycle. The technique is, therefore, also termed 'multiple gated acquisition' or MUGA. The final average at each gate is displayed as one cardiac cycle that can be visualised over and over in an endless loop format like a cineangiogram. Relative end-diastolic and end-systolic cardiac volumes can be calculated simply by subtracting the 'background' activity from the counts obtained in these time intervals. The stroke volume (end-diastolic volume – end-systolic volume) and the 'ejection fraction' (stroke volume/end-diastolic volume) can be calculated. ERNA also permits an assessment of regional contractions of the myocardium. Contraction of segments is graded as normal, hypokinetic (inward motion slightly depressed), akinetic (no motion appreciated), or dyskinetic (paradoxical outward motion in systole). ERNA can be performed during and after supine bicycle exercise (exercise MUGA), when a fall or a failure to increase the resting ejection fraction by more than five per cent, or the appearance of a new wall motion abnormality, or worsening of a pre-existent one, may indicate exercise-induced ischemia.

Perfusion scintigraphy uses a radioactive potassium analogue, thallium-201, as the imaging tracer. Thallium 201 is taken up by a segment of the myocardium in proportion to the amount of blood flow to that segment. An area of deficient uptake appears as a 'cold spot' on the scan and indicates a lack of regional blood supply, usually due to a scar tissue. Thallium imaging is usually performed with exercise when the agent is injected intravenously at peak exercise and an image is acquired immediately. A cold spot on this scan may represent either a scar or exercise-induced ischemia. Hence a second scan is obtained at an interval of two to three hours after the initial scan. If the second scan shows normalisation of the initial cold spot ('redistribution'), then exercise-induced ischemia is the likely explanation. If the defect persists, a third scan is obtained at 24 hours when the defect may disappear occasionally, indicating the presence of 'viable' myocardium. A cold spot in this third scan identifies a myocardial scar. The presence of multiple defects at peak exercise which disappear later, or an increase in uptake in the lung fields suggests multi-vessel coronary artery disease. Newer perfusion agents such as Technetium^{99m} MIBI (methoxyisobutyl isonitrile) are currently being tried due to certain properties which are conducive to better imaging. *Infarct-avid scintigraphy* (also called 'hot spot' scanning) uses Technetium^{99m} stannous pyrophosphate injected intravenously to image the necrotic myocardial cells (in acute myocardial infarction), which selectively take up the tracer. The scan is positive after 24 hours of sustaining an infarction and is more sensitive for transmural infarcts. Anti-myosin scans utilise monoclonal antibodies directed against myosin and the tracer is taken up by necrotic myocytes (e.g. myocarditis or infarction).

ECHOCARDIOGRAPHY

The use of ultrasound in imaging cardiac structure and function is called echocardiography. Cardiac ultrasound examination is divided into M-mode, two-dimensional (2-D), spectral Doppler, colour Doppler, contrast, and transesophageal echocardiography (TEE).

Principle and techniques The *M-mode* echocardiogram is obtained by usually placing a transducer on the chest wall and directing a stationary ultrasound beam at some portion of the heart to obtain an 'ice pick' view of the structures perpendicular to the beam. By changing the direction of the ultrasound beam, echoes for different cardiac structures can be obtained. *Two-dimensional* echocardiography provides real-time spatially correct images of cardiac structures by steering the ultrasound beam through an arc of upto 90 degrees; the images resemble cineangiograms and can be recorded on a videotape. *Doppler* echocardiography uses ultrasonic signals recorded from moving blood within the cardiovascular system. The spectral Doppler signal indicates the velocity, direction and type of flow. Colour Doppler echocardiography is essentially like two-dimensional echocardiography in which the ultrasound signal is coded in colour to indicate the direction of blood flow; flow of blood towards the transducer is coded as red and flow away from the transducer is coded as blue. When there is turbulent blood flow within any chamber or across any valve, a 'mosaic' pattern (of a bright golden colour) is seen. *Contrast* echocardiography is a 2-D examination during which a contrast[1] medium is injected rapidly into the cardiovascular system; this generates microbubbles that produce a cloud of echoes (ultrasonic contrast) within the cardiac chambers. The early appearance of microbubbles in a particular chamber or their appearance in a chamber where they do not normally appear (microbubbles do not traverse the capillary beds) provides evidence of intracardiac shunting. In *transesophageal* echocardiography, a transducer mounted at the end of a fiberoptic probe is introduced into the esophagus and the cardiac structures imaged from a plane posterior to the heart. TEE is extremely useful for imaging the thoracic aorta, for the diagnosis of aortic dissection, prosthetic valves (for evaluating function, regurgitation), endocarditis and its complications, and for visualising the atrial appendages for detecting clots.

Clinical uses (Fig 12.29)

Cardiac structure and function: Echocardiography is used to measure cardiac chamber dimensions, wall thickness, cardiac volumes and left ventricular mass. It provides qualitative and quantitative information about global and regional cardiac systolic function. Doppler studies yield hemodynamic information such as cardiac output, and the patterns of flow across atrioventricular valves can be used to assess cardiac diastolic function.

Valvular heart disease: 2-D echocardiography can be used to directly visualise the cardiac valves and to determine mitral valve area by planimetry. Colour Doppler imaging is useful for visualising turbulence across stenotic valves and abnormal regurgitant flows. A semiquantitative evaluation of valvular regurgitation is provided by the location, shape, direction and size of the regurgitant jet. Doppler echocardiography is valuable for assessing pressure gradients across stenotic valves (calculated using the Bernoulli principle[2]) and for the calculation of aortic and mitral valve areas.

Congenital heart disease: 2-D echocardiography provides information about the position and orientation of the cardiac chambers and great

[1] An agitated solution of saline is an excellent contrast when injected rapidly.

[2] Pressure gradient across a stenotic valve = $4(V_2^2 - V_1^2)$, where V_2 is the velocity distal to the stenosis and V_1 is the velocity proximal to the stenosis.

vessels, and helps to identify anatomical abnormalities. Colour Doppler helps identify intracardiac shunts across the cardiac septa and Doppler studies can define the pressure differences between communicating cardiac chambers. Contrast echocardiography can detect right to left shunting with the use of intravenous injections administered in a proximal upper arm vein.

Ischemic heart disease: 2-D echocardiography is useful for identifying regional wall motion abnormalities either at rest or during exercise (stress echocardiography). Exercise can be performed either on a treadmill or with the infusion of pharmacologic agents such as dobutamine. 2-D echocardiography is useful in identifying complications of myocardial infarction such as ventricular aneurysms or intracardiac thrombi. Colour Doppler examination helps identify postinfarction septal rupture and mitral regurgitation (related to damage to the papillary muscles).

Myocardial and pericardial disease: 2-D echocardiography readily identifies the different types of cardiomyopathies (amyloidosis,[1] dilated cardiomyopathy, hypertrophic cardiomyopathy) and is the test of choice for detecting pericardial effusions. Doppler techniques are valuable for assessing the presence of ventricular outflow obstruction in subjects with hypertrophic cardiomyopathy. Doppler echocardiography is also helpful for differentiating subjects with restrictive cardiomyopathy from those with pericardial constriction and for assessing the physiologic significance of a pericardial effusion prior to the onset of frank tamponade.

Cardiac masses: 2-D echocardiography is used in conjunction with TEE for diagnosing intracardiac masses and for identifying their attachment and their spread.

Aortic diseases: 2-D echocardiography is helpful in identifying sinus of Valsalva aneurysms and aortic coarctation. TEE is the diagnostic procedure of choice for aortic dissection.

[1] A speckled pattern of myocardial echogenicity is very suggestive.

His Bundle Electrocardiography

His bundle electrocardiography is a technique which permits the localisation of the sites of conduction disturbances and helps in determining their severity. In this technique, an electrode catheter is advanced into the right ventricle, under fluoroscopic control, by way of the femoral vein. This electrode catheter is used to record intracavity cardiac potentials. Depolarisation of the low septal right atrium causes a fairly large deflection, designed A wave. A smaller and more rapid biphasic or triphasic deflection is registered on depolarisation of the bundle of His (H spike). This spike is followed by another large deflection (V spike), representing depolarisation of the ventricular myocardium. The *AH interval* (measured from the first rapid deflection of the low atrial electrogram A to the onset of the His bundle deflection H) approximates AV nodal conduction time. The *HV interval* (measured from the onset of the His bundle deflection to the earliest point of ventricular activation) is an indicator of conduction time within the His-Purkinje system. The normal AH interval in adults ranges from 60 to 140 milliseconds and the normal HV interval ranges from 30 to 55 milliseconds. Prolongation of the AH interval reflects delayed conduction within the AV node, whereas prolongation of the HV interval indicates delayed conduction within the His-Purkinje system.

CARDIAC CATHETERISATION AND ANGIOGRAPHY

Cardiac catheterisation is the invasive process of introducing a catheter usually made of polyethylene or its derivatives into the left-sided cardiac chambers (left heart catheterisation) or the right-sided cardiac chambers (right heart catheterisation) by the arterial or venous route respectively, to measure the pressure and the

Fig 12.29

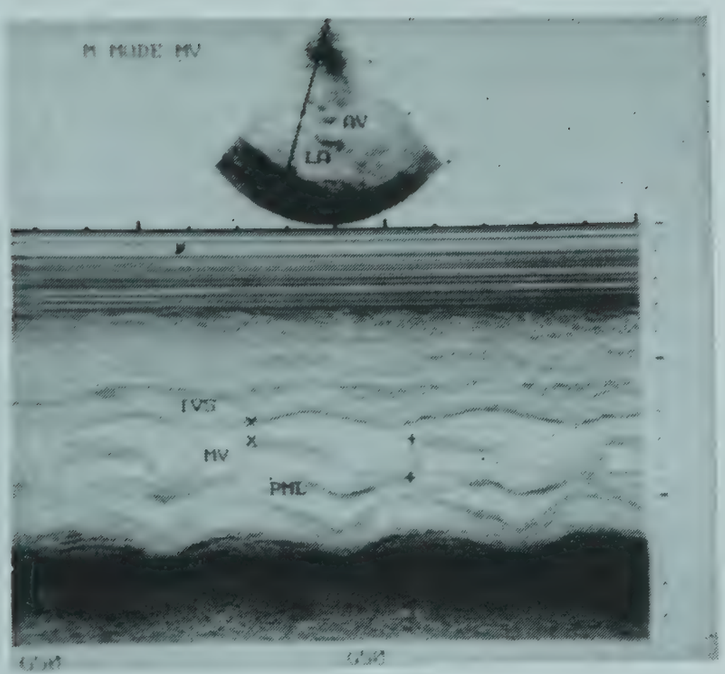


Fig A M mode echocardiographic image (at the level of the mitral valve (MV). The distance between the two (X) signs shows the E point-septal separation (EPSS), that is, the distance between the E point of the mitral valve and the ventricular septum. EPSS when increased suggests ventricular enlargement. The distance between the two (+) signs shows the DE excursion of the anterior mitral leaflet. The DE excursion indicates valve pliability. Note a flat EF slope and a flat motion of the posterior mitral leaflet (PML). This patient had moderate non-calcific mitral stenosis

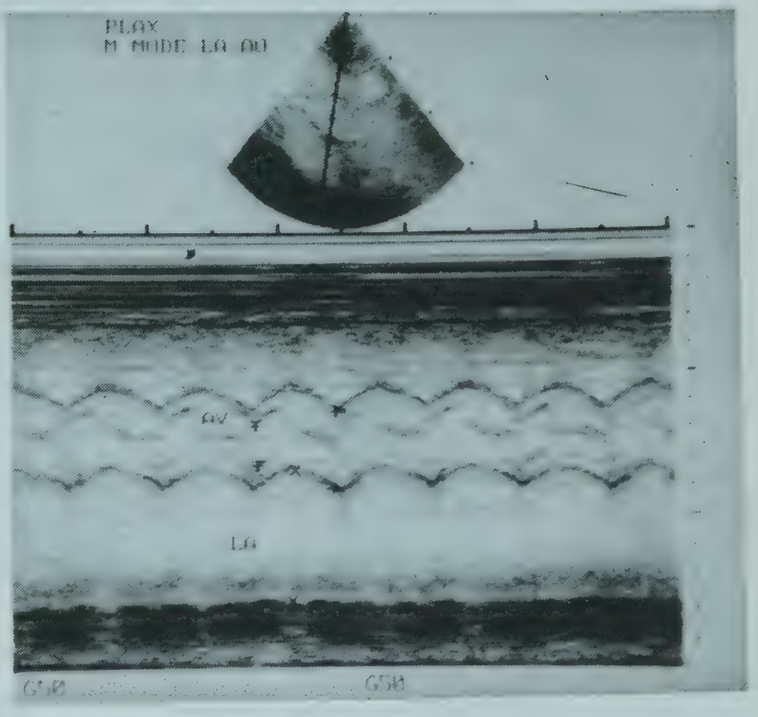


Fig B M-mode echocardiographic image of the left ventricular outflow tract and left atrium of the same patient in A. Note the large left atrium (measured between two points (x) at end-systole) as compared to the aorta (measured between the two points (+) at end-diastole). The aortic leaflets form a systolic box. The aortic cuspal separation (distance between two (∓) is adequate.

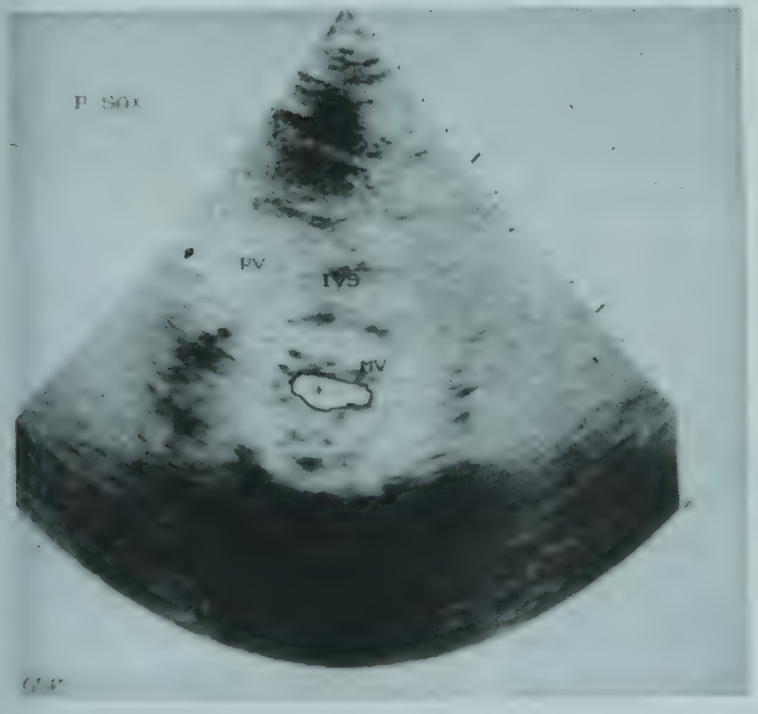


Fig C Two-dimensional echocardiographic image (short axis view) of the mitral valve of the same patient in Fig A and B. The mitral valve area is measured by planimetry (1.2 cm^2 in this case).

oxygen content of blood within these chambers. The procedure can be accomplished by using the femoral or the brachial vessels. Angiocardiography is the visualisation of the cardiac chambers and the arteries and veins by X-ray, following the injection of contrast media for the purpose of defining cardiac anatomy and the direction of blood flow.

Diagnostic use Right and left heart catheterisation can be used to establish the presence of left to right shunts and to quantify them. Catheterisation has also been the gold standard for identifying the presence of valvular heart disease and to assess the severity of various lesions prior to valve surgery. Valvular stenosis can be assessed by the measurement of transvalvular gradients and valve areas can be computed. Left and right ventricular systolic and diastolic pressures and pulmonary artery pressures can be measured. A balloon floatation catheter (Swan-Ganz catheter) can be advanced

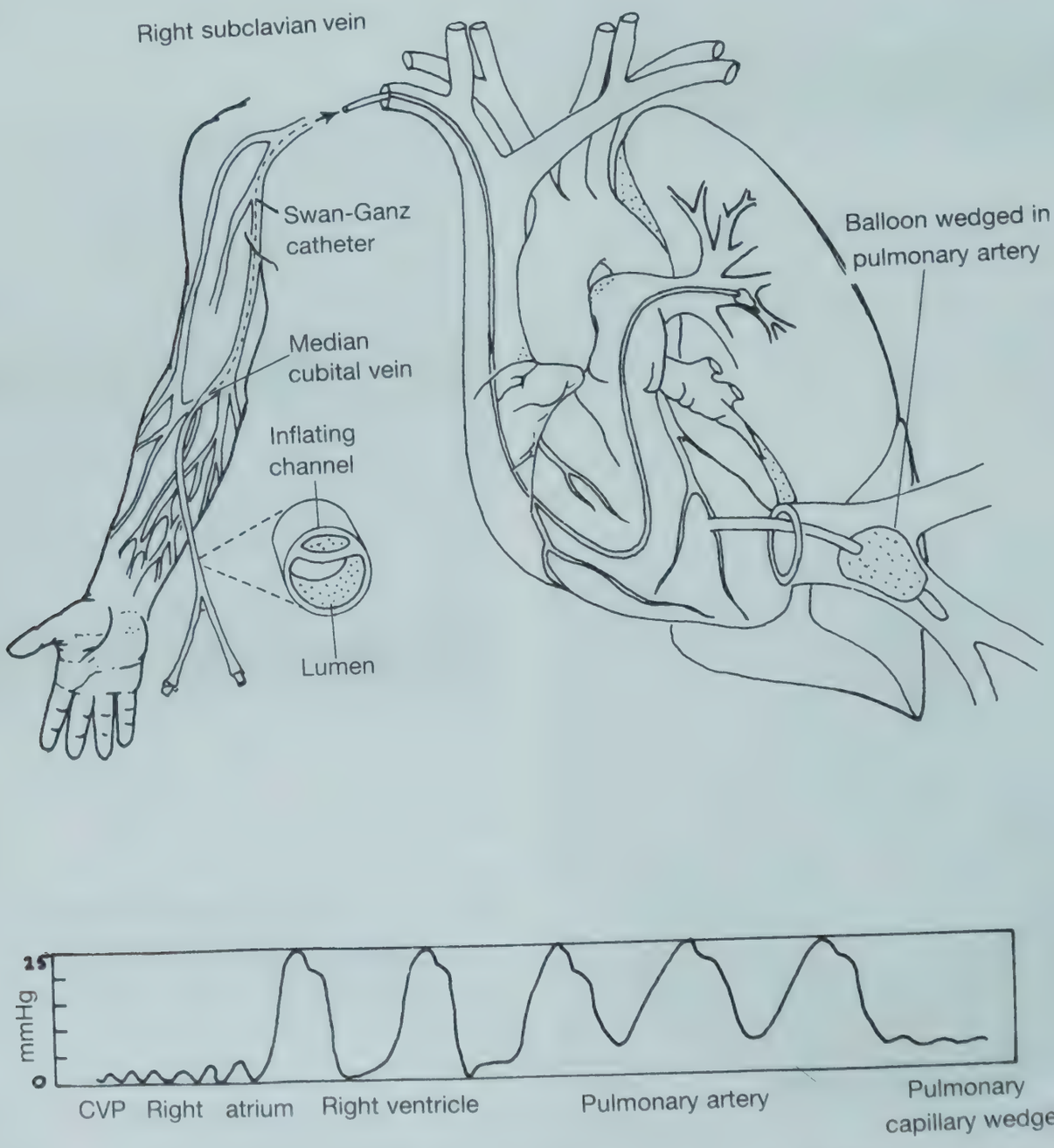


Fig 12.30 Insertion of a Swan-Ganz catheter. The position of the catheter is reflected by the pressure tracings. Capillary wedge pressure is obtained by inflating the balloon.

into the pulmonary artery peripherally (Fig 12.30); the pressure tracing obtained by inflating the balloon represents the pulmonary artery wedge pressure which is the left ventricular filling pressure. Assessment of the left ventricular filling pressures is crucial in the management of the hypotensive patient when the fluid status is clinically unclear.

Angiocardiography is the injection of radio-opaque contrast media into a chamber and following its passage during the cardiac cycle. It can demonstrate shunts and valvular regurgitation. It can also be used to measure left ventricular ejection fraction. Echocardiography as a technique is now so advanced that cardiac catheterisation may not be needed for the diagnosis of simple congenital heart lesions and single valve lesions.

Cardiac catheterisation is associated with a risk of stroke or excess blood loss (0.5%) and a very small risk of death (0.02%).

CORONARY ARTERIOGRAPHY

Coronary arteriography is the gold standard for identifying the presence of coronary atherosclerosis and for assessing its severity. The two main indications for coronary arteriography are: 1) as a diagnostic test to identify atherosclerotic coronary artery disease, and 2) to determine the exact coronary anatomy in patients with coronary artery disease to determine the need and feasibility for coronary angioplasty, coronary artery bypass surgery, or medical therapy. A left ventricular angiocardiogram is usually performed at the same sitting and permits the assessment of left ventricular systolic function and wall motion abnormalities. The procedure involves introducing a catheter through the femoral artery, engaging the ostium of each coronary artery and injecting radio-opaque contrast media. The procedure has a low complication rate; death occurs in fewer than 0.02 per cent of patients and less than 0.5 per cent suffer a myocardial infarction, coronary artery dissection, stroke or blood loss.

ENDOMYOCARDIAL BIOPSY

In this procedure a catheter biopsy forceps called a *bioptome* is introduced through the transvenous route and positioned against the interventricular septum; several pieces of myocardial tissue can then be obtained under fluoroscopic or echocardiographic guidance. Myocardial biopsy is performed routinely after cardiac transplantation to detect cardiac allograft rejection. The procedure has also been used to diagnose acute myocarditis, glycogen storage disease, hemochromatosis, cardiac sarcoidosis, amyloidosis and anthracyline toxicity. Cardiac tamponade is a potential complication occurring in 0.1 per cent of patients.

CARDIAC MAGNETIC RESONANCE IMAGING (MRI)

Cardiac MRI can provide precise, detailed, quantitatively accurate information about cardiac structure and function. MRI is, however, expensive, and the machines are not portable; the technique has limited utility in the sick patient. Cardiac MRI has utility in four main areas: 1) visualisation of cardiovascular structure in three dimensions (complex congenital heart disease); 2) characterisation of cardiac and pericardial tissues; 3) the assessment of global and regional cardiac function, determining the degree of valvular regurgitation and shunts, estimation of ventricular ejection fraction, stroke volume and cardiac output, and 4) diagnosing thoracic aortic diseases (aneurysms and dissection). Cardiac MRI is contraindicated in patients with cardiac pacemakers and certain valve prostheses.

KEY CONCEPTS

Chest X-ray

- The cardiac size is assessed by the cardiothoracic ratio (CTR= sum of maximum cardiac width either side of midline ÷ maximal diameter of bony thorax; normal <0.50). In the frontal plane, the left heart border is formed from above downwards by the aortic knuckle, MPA segment, LA appendage area (concavity), and the LV; the right heart border is formed by the SVC and the RA.
- LA enlargement is evidenced by a widening of the carinal angle and by the appearance of a double density on the right heart border. LA appendage enlargement results in the filling up of the normal concavity on the left heart border. When the MPA is also enlarged (as in MS), the left heart border is straight.
- LV enlargement appears as an increase in CTR with an apical LV contour. RV enlargement is best seen as an increase in the retrosternal translucency on a lateral chest X-ray; in the frontal plane, it appears as an increase in the CTR with a rounded cardiac apex.
- The size of the MPA and LPA may be an index of PA pressures; in pulmonary arterial hypertension, there are large hilar arteries with peripheral pruning. Pulmonary venous hypertension manifests with prominent upper lobe pulmonary veins. Interstitial edema appears as prominent interlobular septa (Kerley B lines). Pulmonary plethora (>3 end-on vessels) is seen in left to right shunts. Pulmonary oligemia is seen in right to left shunts, pulmonary embolism, severe RV failure and tamponade.

Electrocardiography

- The ECG represents the electrical activity of the heart recorded on 12 leads (6 frontal plane leads (3 bipolar and 3 unipolar) and 6 precordial leads (horizontal plane)).
- The bipolar leads are related by the equation II = I + III, while the augmented limb leads are related by the equation $aV_R + aV_L + aV_F = 0$.
- The ECG consists of 3 waves; the P wave represents atrial depolarisation, the QRS complex represents ventricular depolarisation, while the T wave represents ventricular repolarisation. The PR interval indicates the time for conduction of impulse from the SA node to the ventricular muscles while the QT interval indicates the time for completing ventricular systole and repolarisation.
- The axis of the QRS complex in the hexaxial frontal plane varies from +90° to −30°; an axis beyond −30° indicates left axis deviation, while an axis beyond +90° indicates right axis deviation.
- The ECG is useful for the diagnosis of coronary events, arrhythmias, electrolyte status, myocardial and pericardial disease. Myocardial injury is indicated by ST segment elevation, myocardial ischemia by ST segment depression and myocardial necrosis by pathological q waves. When there is a major interruption of cardiac impulse conduction through parts of the His-Purkinje system, a bundle branch block appears on the ECG. In a complete bundle branch block, the QRS complex is >0.12 sec in duration. In right bundle branch block, an M-shaped QRS complex appears in V_1 while a W-shaped complex is noted in V_6. In left bundle branch block, a W-shaped QRS compex appears in V_1 while an M-shaped configuration is noted in V_6.

Cardiac stress testing

- In the simplest form stress testing involves an exercise work load performed on a treadmill with monitoring of the surface ECG; a displacement of the ST segment by ≥1 mm (measured 0.08 sec after the J point) which is horizontal or downsloping in configuration is suggestive of ischemic heart disease. The test is useful for the diagnosis of coronary artery disease and for prognostication (risk stratification after an MI).
- The stress thallium, SPECT thallium and dobutamine echocardiogram are alternatives to the ECG-stress test.

Cardiac scintiscans

- Radionuclide scans of the heart are useful for the evaluation of myocardial function (MUGA), myocardial ischemia (stress thallium), myocardial infarction (technetium^{99}-labelled red cells and thallium scans) and myocardial metabolism (PET scans).

Echocardiography

- An M-mode scan provides an ice-pick view of the heart which is useful for making quantitative cardiac measurements. A two-dimensional scan enables visualisation of the cardiac chambers, wall thickness and the valve morphology. Doppler studies help to assess flow across the cardiac valves, cardiac septa and the great vessels. The transesophageal echocardiogram provides an additional window to evaluate the heart and the aorta.

Cardiac catheterisation

- In this technique, intravascular catheters are introduced to measure intracardiac pressures and oxygen saturation. Combined with injection of radiographic contrast (angiocardiography), the technique is useful for assessment of valve function, myocardial function and intracardiac shunts. Coronary angiography remains the gold standard for the diagnosis of atherosclerotic obstructive coronary artery disease.

Other investigations

- Ambulatory cardiac ECG monitoring (Holter monitor) is a useful test for documenting arrhythmias and ischemic episodes.
- Ambulatory blood pressure monitoring is presently an investigational tool useful for identifying the degree of blood pressure control on medications in known hypertensives, and for documenting the extent of elevation of blood pressure in labile hypertensives.

12.4 Congestive heart failure

Congestive heart failure is a clinical syndrome which results from an abnormality of cardiac function, either due to an inability of the heart to pump blood forward at a volume adequate to meet the metabolic needs of the tissues (forward failure), or to distend sufficiently during diastole thereby leading to circulatory congestion (backward failure). Congestive heart failure is associated with an increase in atrial pressures, a diminished exercise tolerance, ventricular arrhythmias and a shortened life expectancy. The abnormality in cardiac function may be due to an abnormality of the myocytes themselves (myocardial failure) or to some other structural abnormalities of the valves or of the pericardium, such as valvular stenosis or constrictive pericarditis. Congestive heart failure refers to a state of peripheral or pulmonary congestion associated with heart failure.

Pathophysiology Myocardial failure may be due to a quantitative localised loss of the amount of functioning cardiac myofibres, such as in heart failure associated with a large myocardial infarction. It may also be due to a generalised abnormality in cardiac myocyte function, as seen in dilated cardiomyopathy. The precise mechanism of abnormal myocyte function in heart failure is controversial. Possible mechanisms include a reduction in myofibrillar ATPase or a defect in the ability of the sarcoplasmic reticulum to pump calcium, or alterations of cardiac myocyte mitochondrial function. Heart failure is also associated with a depletion of myocardial norepinephrine stores and a decrease in local production of

Table 12.13 Causes of heart failure

A. Systolic failure

1. Intrinsic myocardial disease
   a. Cardiomyopathy
   b. Myocarditis
   c. Coronary artery disease
   d. Systemic disease
2. Increased work load
   a. Pressure overload (hypertension, aortic stenosis)
   b. Volume overload (aortic regurgitation, mitral regurgitation, shunts)
   c. High output (A-V fistulae, beriberi, thyrotoxicosis)

B. Diastolic failure

1. Acute ischemia (coronary artery disease)
2. Left ventricular hypertrophy (systemic hypertension, hypertrophic cardiomyopathy)
3. Restrictive heart disease

C. Precipitating factors

1. Dietary indiscretion (increased salt intake)
2. Non-compliance with drugs
3. Intercurrent infection
4. Thyrotoxicosis
5. Pulmonary embolism
6. Myocardial depressant drugs
7. Arrhythmias
8. Endocarditis or myocarditis
9. Pregnancy
10. Progression of native disease (recurrent myocardial infarction, worsening valvular disease)

norepinephrine within the myocytes. The causes of heart failure are shown in Table 12.13. It may be related to systolic dysfunction of the myocardium, or due to a diastolic dysfunction of the myocardium.

As heart failure develops, the cardiac output decreases, and several compensatory mechanisms come into play to help maintain a normal cardiac output and to maintain normal tissue perfusion in the presence of decreased myocardial function. The first mechanism is the Frank-Starling mechanism according to which the force of contraction of the cardiac muscle depends on its initial length as depicted in Fig 12.31. As the ventricular end-diastolic volume (*preload)* increases, ventricular performance is enhanced. Factors which shift the Frank-Starling curve upward and to the left include sympathetic nervous stimulation by circulating catecholamines and positive inotropic agents such as digitalis. Factors which shift the Frank-Starling curve downward and to the right include hypoxemia, acidosis and drugs that depress myocardial function. An additional local compensatory mechanism is myocyte hypertrophy and remodelling of myocytes in an attempt to maintain cardiac output and to pump more vigorously. The third compensatory mechanism that is initiated in heart failure is the activation of several neurohormonal systems. The effects include activation of the sympathetic nervous system with increased plasma catecholamine levels, activation of the renin-angiotensin aldosterone system, increased production of the antidiuretic hormone and release of atrial natriuretic peptide (ANP). These changes are primarily meant to be compensatory and to defend against traumatic hypovolemia and dehydration, and are potentially capable of restoring blood pressure under these circumstances. However, activation of the neurohormonal system in heart failure can have adverse affects. These hormones all add to increased systemic vascular resistance and promote salt and water retention (except ANP). The increased systemic vascular resistance represents an increase in cardiac *afterload.* Afterload refers to the tension generated in the left ventricular wall in order to open the aortic valve and discharge the stroke volume into the systemic circulation. Eventually, as heart failure progresses, the compensatory mechanism can no longer maintain cardiac function and the clinical syndrome of heart failure emerges.

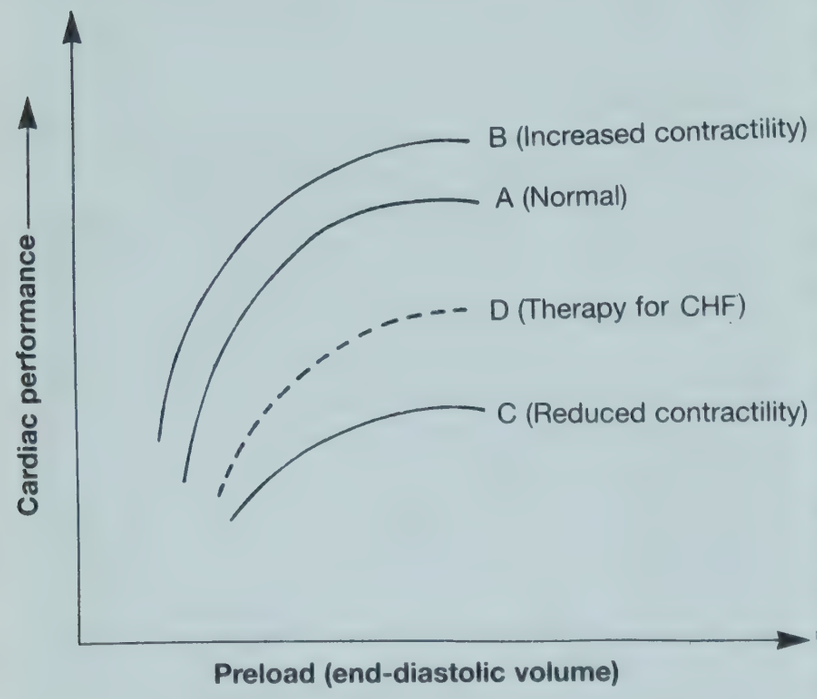


Fig 12.31 Frank-Starling curves showing the interrelationship of ventricular contractility and end-diastolic volume

Clinical cardiac failure involves an element of both backward cardiac failure and forward cardiac failure. Backward failure refers to blood damming up behind one or both ventricles and refluxing into the atria, and from there into the pulmonary or the systemic veins; the ventricle either cannot pump its contents forward normally in systole, or it cannot distend normally in diastole to accommodate the venous return. Symptoms, therefore, result from an increase in systemic venous pressures in right ventricular failure; this results in transudation of fluid into the subcutaneous tissues, the mesentery, the peritoneum and the capsule of the liver. Symptoms in left ventricular failure result from an increase in pulmonary venous pressure which

in turn results in an increase in pulmonary capillary pressures. This increase results in transudation of fluid into the interstitium of the lung and eventually into the alveoli itself; this is known as *pulmonary edema.*

'Forward' cardiac failure refers to the inability of the heart to pump an adequate amount of blood into the systemic arterial circulation resulting in symptoms of under perfusion of various vital organs such as, the skeletal muscles, the central nervous system and the kidneys. Reduced perfusion of the brain results in mental confusion, reduced perfusion of the skeletal muscles results in exercise intolerance and fatigue, whereas reduced renal perfusion results in an increased sodium-and-water retention, leading in turn to an increase in extracellular fluid levels and tissue congestion. Two other terms used in the context of cardiac failure are *low output cardiac failure* and *high output cardiac failure.* Low output cardiac failure is characterised by a reduced stroke volume, peripheral vasoconstriction with cold and pale extremities, and reduced pulse pressure. Low output cardiac failure is the most common form of heart failure and is usually due to an ischemic, valvular, hypertensive, congenital or a cardio-myopathic process. High output cardiac failure on the other hand is characterised by widened pulse pressure and peripheral vasodilation with warm and flushed extremities. The causes of such high output cardiac failure include anemia, thyrotoxicosis, beriberi, arteriovenous fistulae and Paget's disease of the bone. High output cardiac failure states are characteristically associated with a reduced arteriovenous oxygen difference.

Systolic cardiac failure is usually associated with an inability of the ventricles to pump out blood from their cavities in systole. However, cardiac failure may be diastolic in origin. Diastolic cardiac failure refers to the inability of the ventricle to fill up with or accept blood. This abnormality is typically seen in stiff ventricles which fail to relax adequately to accept blood from the atria during diastole. Consequently, the ventricular diastolic pressure increases and correspondingly the atrial pressures are also increased leading to systemic or pulmonary vascular congestion. Such diastolic cardiac failure can even be a transient event; patients with coronary artery disease may develop pulmonary edema during episodes of ischemia (known as *flash pulmonary edema).* The other cause of diastolic heart failure includes hypertrophied ventricles either due to hypertensive heart diseases or due to a hypertrophic cardiomyopathy. It is also seen in patients with restrictive cardiomyopathies where there is a replacement of the myocytes by scarred tissue or fibrillar material.

Symptoms The major clinical symptoms of left-sided heart failure include exertional dyspnea, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea, fatigue, nocturia and mental confusion. Dyspnea is the sensation of breathlessness which accompanies left-sided heart failure. It is due to an increased work of breathing consequent to lungs which are stiff as a result of interstitial edema of varying amounts. *Orthopnea* is the dyspnea that occurs while the patient is recumbent and which is relieved by standing or sitting up. It occurs whenever there is redistribution of fluid from the dependent parts of the circulation, such as the leg veins, to the thorax, in the recumbent position. The severity of orthopnea is estimated by asking the patient how many pillows he places under the head.

Paroxymal nocturnal dyspnea is an extreme form of orthopnea which awakens a patient from sleep with a sense of severe breathlessness; it is often unrelieved by sitting upright and forces the patient to go up to a window for fresh air. The pathophysiologic hallmark of paroxysmal nocturnal dyspnea is interstitial pulmonary edema which is often associated with wheezing and bronchospasm. Hence there is a need for distinguishing cardiac asthma from a pulmonary cause of dyspnea in patients with chronic

obstructive airway disease. Cardiac asthma tends to be more sudden in onset and occurs in patients with known left ventricular dysfunction; it is usually not associated with sputum production, and often there is no history of preexisting pulmonary disease.

Paroxysmal nocturnal dyspnea therefore represents a state of incipient pulmonary edema. Frank pulmonary edema which is associated with transudation of fluid into the alveoli is known as *alveolar edema.* It is the most severe form of breathlessness associated with left ventricular failure. The patient is extremely short of breath at rest, agitated, tachypneic and often has pink frothy sputum.

The common causes of right-sided heart failure are listed below.The commonest cause of right-sided heart failure is left-sided heart failure. The symptoms of predominantly right-sided heart failure are due to elevation of the systemic venous pressures and the resultant congestive circulatory state. There may be dependent edema at the ankles in the ambulatory patient, and in the sacral area in the bedridden patient. Right upper quadrant pain in the abdomen is a feature of right-sided heart failure and is related to the stretching of the hepatic capsule from liver engorgement as a result of passive hepatic venous congestion. Anorexia and nausea are related to congestion of the mesentery and the gastric and intestinal mucosa. Pulmonary symptoms are often relieved when left-sided heart failure results in right-sided heart failure. Amelioration of dyspnea may then occur in these patients.

Table 12.14 Causes of right heart failure

A. With pulmonary hypertension

1. Postcapillary pulmonary hypertension
   - Left ventricular failures of any cause
   - Mitral stenosis
   - Pulmonary venous obstruction
2. Precapillary pulmonary hypertension
   - Primary pulmonary hypertension
   - Eisenmenger syndrome
   - Cor pulmonale (of any etiology)
   - Pulmonary embolism

B. Without pulmonary hypertension

1. Pulmonic valve stenosis
2. Right ventricular myocardial infarction
3. Right ventricular cardiomyopathy
4. Tricuspid stenosis
5. Tricuspid regurgitation (trauma, endocarditis, Ebstein's anomaly of the tricuspid valve)

Signs of Cardiac Failure

Tachycardia is an important sign of left-sided and right-sided heart failure. It is a compensatory mechanism whereby the heart attempts to maintain cardiac output in the setting of a reduced stroke volume. Pulsus alternans is also a manifestation of left ventricular failure. Pulsus alternans is characterised by a regular rhythm in which there is an alternation of strong and weak contractions of the pulse detected by palpation. This phenomenon is due to an alternation of the stroke volume produced by hypocontractile cardiac myocytes. Occasionally, the patient with cardiac failure may manifest Cheyne-Stokes respiration. This pattern of respiration is characterised by alternating periods of apnea and hyperpnea.

On cardiac auscultation, the first sound is often soft. The second heart sound may be paradoxically split, which reflects a late aortic component of the second heart sound due to a prolonged left ventricular ejection time. The pulmonic component of the second heart sound may be accentuated with the onset of pulmonary arterial hypertension. A protodiastolic or S_3 gallop is a common sign of left ventricular failure. This sound occurs due to a rapid deceleration of ventricular inflow that occurs immediately after the early filling phase of the ventricle. When a stiff or hypertrophied ventricle underlies the left ventricular failure, a fourth heart sound (a presystolic gallop) may be heard due to forceful contraction of the atrium that pumps blood into a stiff non-compliant ventricle. As ventricular dilatation progresses,

the anulus of the atrioventricular valves may dilate and result in secondary mitral or tricuspid regurgitation. The signs of right ventricular failure include jugular venous distension, a tender hepatomegaly, positive hepatojugular reflux, peripheral edema and ascites. With right heart failure, as tricuspid regurgitation develops, there may be a prominent systolic V wave in the jugular venous wave form and this can be palpated as systolic pulsations of an enlarged and tender liver. The acutely sick patient with acute heart failure appears in respiratory distress, is tachypneic, pale, and has cold peripheral extremities. There may be evidence of central or peripheral cyanosis. Examination of the chest may reveal moist rales at the lung bases. The lung bases may be dull on percussion, indicating an associated pleural effusion.

Investigations Important clinical investigations in the patient with heart failure include a chest X-ray. The typical chest X-ray feature of congestive heart failure is an enlarged cardiac silhouette, measured in terms of what is called the cardiothoracic ratio (see section 12.3). Cardiomegaly is suggested by a cardiothoracic ratio greater than 0.5. The appearance of the lung fields provides an estimate of pulmonary capillary pressure. In a normal chest X-ray, the apices of the lung are less well-perfused as compared to the bases, due to the effect of gravitational force. As the pulmonary capillary pressures are elevated to a level of 15–20 mmHg the apical and basal perfusions equalise: this phenomenon is called *equalisation*. As the pulmonary capillary pressures are elevated upto 21–24 mmHg the upper lobe pulmonary veins become *more* prominent than the lower lobe pulmonary veins (*cephalisation*). With the pulmonary capillary pressures in the range 24–26 mmHg interstitial pulmonary edema and Kerley B lines (that is, edematous interlobular septa) become evident. As the pulmonary capillary pressures increase beyond this, alveolar edema becomes evident as fluffy intraalveolar exudates, typically seen in the perihilar region of the cardiac silhouette. This gives the typical '*bat's wing*' *radiographic appearance* of acute pulmonary edema. The surface ECG helps in a patient with heart failure in defining certain etiologies such as active ischemia, or present or previous infarction, and the presence of ventricular hypertrophy (which is an important clue for diastolic heart failure).

An echocardiogram is especially useful in assessing both the severity of heart failure as well as its etiology. It also helps in serial evaluation of the effects of therapeutic measures on cardiac function. Radionuclide ventriculography is another useful non-invasive technique for assessing ventricular function. Blood chemistry tests are often abnormal in patients with congestive heart failure. The levels of liver enzymes like SGOT, SGPT and plasma bilirubin are often elevated in patients with right-sided heart failure, usually reflecting centrilobular hepatic venous congestion. Urine analysis may reveal the presence of proteinuria. With reduced renal perfusion, the blood urea levels may become elevated, reflecting a state of prerenal azotemia.

Serum electrolytes tend to be normal in mild congestive heart failure. With severe heart failure and extensive peripheral edema, there may be dilutional hyponatremia. Serum potassium levels may be low as a result of therapy with thiazide diuretics. Once the patient has been stabilised with medical treatment, further investigations may be indicated. Cardiac catheterisation is useful in identifying the causes of heart failure and assessing the severity of associated valvular abnormalities. Coronary angiography may be undertaken to diagnose significant coronary artery disease. When congestive heart failure is suspected to be due to acute myocarditis, cardiac catheterisation with *endomyocardial biopsy* may be indicated.

Natural history and prognosis The prognosis of heart failure is directly related to its severity. Thus, though the average five-year mortality rate for heart failure is about 50 per cent, in

patients with severe heart failure the one-year survival rate may be only 50 per cent. Sudden death accounts for about a third of deaths in subjects with heart failure.

Management of acute pulmonary edema The goal of treating acute cardiogenic pulmonary edema is to improve oxygenation and to reduce symptoms due to elevated pulmonary capillary pressures. The patient should be sitting upright, preferably with his legs dangling by the side of the bed. This position serves to increase venous pooling, thereby reducing central venous pressures. It also improves pulmonary ventilation-perfusion matching. Oxygen should be administered by nasal prongs or by a face mask at a high flow rate, except in patients with chronic obstructive airway disease who have evidence of carbon dioxide retention. A large-bore intravenous cannula should be placed for access to circulation for the prompt administration of medication. Intravenous morphine is immediately administered in doses varying from 2–10 mg intravenously. Morphine reduces ventricular preload as well as ventricular afterload. It allays anxiety and thereby reduces sympathetic activation which is a frequent concomitant of acute pulmonary edema. The relative contraindications for the administration of morphine include the presence of severe coexisting pulmonary disease, hepatic failure and myxedema. Signs of respiratory depression must be sought, and morphine antagonists naloxone or nalorphine hydrochloride should be readily available. Intravenous furosemide in a dose varying from 40–100 mg may be administered to help relieve symptoms of acute pulmonary edema. A lower dose of furosemide is used if the patient does not take diuretics chronically or if the blood pressure is low. Furosemide acts immediately by causing renal arterial dilation. It causes diuresis 10–30 minutes after administration with a peak effect in about one hour. If the patient has a systolic blood pressure greater than 95 mmHg, sublingual or intravenous nitroglycerin may be administered to reduce ventricular preload. Sublingual nifedipine may be administered to reduce ventricular afterload. A chest X-ray is obtained in these patients, often to seek an underlying chest infection as a precipitating factor. A 12-lead ECG should similarly be recorded to seek for acute ischemia or injury as a contributory factor to the acute pulmonary edema.

Treatment of chronic heart failure The first step in the treatment of chronic heart failure is to determine its origin and to seek correctable factors. Thus, patients with valvular abnormalities may benefit from surgical correction of the valvular lesions. Similarly, abstinence from alcohol is helpful in alcoholic cardiomyopathy, and treatment of hypertension is beneficial to patients with hypertensive heart disease. A careful search must be made for the presence of precipitating causes of congestive heart failure listed earlier. Useful general measures in the treatment of patients with congestive heart failure include dietary salt restriction, and reduction of physical and emotional stress. Reduction of daily dietary sodium intake to 2 g is usually sufficient. A further reduction in dietary sodium intake is possible but may result in an insipid diet and consequent inadequate caloric intake. Fluid restriction should be implemented especially in patients with dilutional hyponatremia and peripheral edema. Restriction of oral fluids to about 1.5 litres per day is usually adequate. Patients with severe heart failure require pharmacologic therapy in addition to the general measures discussed above. There are three broad categories of drugs for congestive heart failure: 1) inotropic agents, 2) diuretics, and 3) vasodilators.

Of these three agents, the choice of any agent is based on the severity of clinical symptoms and the results of clinical studies which are available in this area. The only agents which have been shown to prolong survival in patients with heart

failure are vasodilators. Diuretics are the first line of treatment in patients with obvious pulmonary or peripheral congestion.

Inotropic agents:

1. Digitalis: Digitalis is a steroid glycoside which has a positive inotropic effect on the heart by virtue of its action of inhibiting the enzyme sodium-potassium-ATPase within the cardiac myocytes. This results in elevated intracellular sodium concentrations which leads to an increase in calcium influx by way of the sodium-calcium exchange mechanisms. The increased availability of cytosolic calcium results in the activation of contractile elements and forceful contraction. Digoxin is the most widely used digitalis preparation. Eighty per cent of oral digoxin is absorbed and it is predominantly excreted by the kidney. In patients with normal renal function, the average half-life of digitalis is 36 hours. The average loading dose of digitalis is 1.25–1.5 mg which can be given as 3–4 divided doses over a period of 24 hours. The intravenous loading dose is usually 0.75 mg given as 3 or 4 divided doses over 24 hours in an adult. Therapeutic digoxin levels can be achieved in about a week when an oral maintenance dose of 0.25 mg per day is given without a loading dose. A lower maintenance dose is used in patients with significant renal impairment.

Although digitalis does not increase the cardiac output in normal persons, it increases the cardiac output significantly in patients with heart failure. Digitalis results in an overall reduction of peripheral vascular resistance due to an improvement in the cardiac output in patients with heart failure. There is no doubt that digitalis is extremely useful in the treatment of patients with heart failure and atrial fibrillation with a rapid ventricular response. The role of digitalis in treating heart failure in patients with normal sinus rhythm has been controversial. Recent studies have demonstrated conclusively that patients with chronic severe heart failure, dilated left ventricles, reduced ejection fraction and clinical presence of a third heart sound are benefited by treatment with digitalis. Digitalis is of no value in patients with chronic obstructive airway disease and cor pulmonale in the absence of right ventricular failure. Similarly, digitalis is not beneficial to patients with mitral stenosis who are in normal sinus rhythm and do not have manifest right ventricular failure. Digitalis can be harmful in patients with hypertrophic obstructive cardiomyopathy, in whom, it can accentuate the left ventricular outflow tract obstruction. Digitalis can also be harmful in patients with the Wolff-Parkinson-White syndrome, especially in the subset of patients with a short refractory period of the accessory pathway.

Digitalis toxicity occurs in 10–25 per cent of hospitalised patients receiving digitalis. In adults, the therapeutic serum digoxin levels are 0.5 to 2 ng/ml. In the presence of clinical toxicity due to digitalis, the serum digoxin levels are usually more than 2 ng/ml. Conditions which predispose to digitalis toxicity include old age, renal insufficiency, electrolyte imbalance (hypokalemia, hypomagnesemia), hyperthyroidism and acute or chronic pulmonary diseases.

The clinical manifestations of digitalis toxicity may be non-cardiac or cardiac. The non-cardiac manifestations include anorexia, nausea and vomiting. They also include symptoms such as fatigue, drowsiness, visual complaints such as hazy vision and yellow halos around objects. Cardiac manifestations of digoxin toxicity are primarily in the form of brady- and tachy-arrhythmias. Ventricular premature depolarisation, junctional tachycardia and varying degrees of second and third degree of atrio-ventricular nodal blocks may occur. Arrhythmias particularly characteristic of digoxin toxicity include paroxysmal atrial tachycardia with varying AV block, bidirectional ventricular tachycardia and regularisation of ventricular rate in atrial fibrillation. The treatment of digoxin toxicity includes immediate discontinuation of the drug, correction of precipitating factors (especially dyselectrolytemia) and continuous

ECG monitoring. Digitalis-induced ectopic ventricular arrhythmias can be effectively treated with phenytoin. Phenytoin is given intravenously as a loading dose of 100 mg infused slowly over five minutes, followed by a maintenance dose of 400–600 mg per day. Lidocaine is also an effective alternative for the treatment of ventricular arrhythmias due to digoxin toxicity. Atropine can be effective in treating sinus bradycardia, AV block or sino-atrial blocks. Temporary transvenous pacing is occasionally required in patients with an extremely slow ventricular rate and advanced AV block. Potassium replacement is generally indicated for patients with hypokalemia in the absence of conduction abnormalities. The serum potassium should be maintained in the high normal range. Rapid reversal of life-threatening digoxin intoxication can be effectively treated with intravenous digoxin-specific F_{ab} antibody fragments; 40 mg of the latter neutralises approximately 0.6 mg of digoxin. These antibody fragments, however are not routinely available in India and are expensive. Drug interactions with digoxin are frequent and must be borne in mind. Drugs which impair digoxin absorption and thereby decrease bio-availability of the drug include cholestyramine, antacids and kaolin-pectin. Drugs which increase serum digoxin levels include antibiotics such as erythromycin and tetracycline (which limit the intestinal metabolism of digoxin by bacterial flora), and quinidine, verapamil, amiodarone and spirono-lactone (which decrease tubular secretion of digoxin).

2. Non-digitalis inotropic agents

a. Sympathomimetic agents:

These are potent inotropic agents primarily used to treat severe heart failure. The beneficial effects, as well as the adverse effects of this class of drugs is mediated by stimulation of myocardial adrenoceptors. Dopamine is an endogenous catecholamine with a positive intropic effect. At a dose 1–3 μg/kg/min, dopamine exerts a selective vasodilatory effect on renal arterioles. At an infusion dose of 2–5 μg/kg/min dopamine increases myocardial contractility by β_1 adrenoreceptor stimulation and decreases peripheral vascular resistance by its effect on vascular dopaminergic receptors. At infusion doses of 5–10 μg/kg/min per minute, dopamine may be deleterious because it increases peripheral vascular resistance due to stimulation of alpha adrenoreceptors.

Dobutamine is a synthetic amine that increases cardiac output by selectively stimulating β_1 cardiac adrenoceptors at an infusion dosage of 2–5 μg/kg/min. Dobutamine, unlike dopamine, does not directly affect renal blood flow, has a less marked arrhythmogenic effect and does not cause excessive tachycardia. Patients with chronic refractory heart failure are often benefited by intermittent in-hospital infusion of dobutamine intravenously for 48–72 hours.

b. Phosphodiesterase inhibitors:

Agents in this category of drugs are also called inodilators. They have a positive inotropic effect by virtue of increasing intracellular cyclic AMP in the cardiac myocytes and also produce peripheral vasodilation. Amrinone is a prototype of this group of drugs, but has the disadvantage of requiring intravenous administration and has potential side effects which include thromobocytopenia. Long term oral amrinone has failed to demonstrate a sustained improvement in cardiac function. Milrinone is a congener that is more potent than amrinone and does not have the thrombo-cytopenic side effect. Clinical trials of milrinone in heart failure have, however, been dis-appointing, being associated with decreased survival and increased risk of ventricular arrhythmias.

Beta-blocking agents:

Paradoxically, a low dose of beta-blockers can result in clinical improvement in patients with congestive heart failure. The mechanisms for these beneficial effects include an upgrading of

the down regulated beta adrenoceptors in congestive heart failure. Administration of these agents, however, requires extreme care and the use of very low doses with careful titration in a hospital setting. Carvedilol, a vasodilatory beta-blocker, has yielded promising results.

Diuretic agents:
Diuretics remain a cornerstone in the treatment of heart failure. They increase urine flow and sodium excretion by the nephrons. The reduction of sodium and water reabsorption results in a reduced ventricular preload and manifests as an improvement in congestive symptoms. A careful assessment of the patient's weight and a record of fluid intake and output are essential during the initiation and the maintenance of therapy with diuretic agents. The optimum goal of therapy should be a net loss of 0.5–1 kg body weight per day. A more rapid diuresis can result in depletion of intravascular volume with consequent hypotension and a decreased renal perfusion. A classification of diuretic agents and their sites of action and dosage are shown in Table 12.15. Thiazide diuretics are the agents of choice in patients who need a mild diuresis and who have normal renal function. Loop diuretics are the preferred agents in patients who require significant diuretics, especially in the presence of markedly decreased renal function. Potassium-sparing diuretics are used in combination with thiazides or loop diuretics in order to maintain normal serum potassium levels. They are particularly useful in patients with predominant ascites as a manifestation of heart failure.

Vasodilators:
Vasodilators are the only class of drugs which have been shown to prolong survival in patients with heart failure. A classification of vasodilator drugs is shown in Table 12.16. The rationale for treatment of heart failure with vasodilators is that the state of heart failure is accompanied by neurohumoral activation which results in inappropriate venous and arteriolar constriction. The venodilators increase venous capacitance; this results in redistribution of blood flow from the pulmonary circulation into the systemic circulation. The ventricular preload is reduced and therefore these agents are most beneficial in patients with elevated left ventricular filling pressures. However, caution should be exercised in using these drugs in patients with reduced preload because a further reduction in ventricular filling pressures can lead to a decrease in cardiac output. Arterial vasodilators reduce systemic vascular resistance and thereby improve cardiac output. These drugs are most useful in patients with heart failure caused by severe hypertension, myocardial infarction and volume overload conditions like regurgitant valvular lesions (mitral or aortic regurgitation) with markedly elevated systemic vascular resistance. Contraindications to vasodilator therapy include conditions with valvular stenosis (aortic stenosis), and restrictive and hypertrophic cardiomyopathies. Vasodilators may be administered parenterally in patients with severe heart failure and hemodynamic instability. Oral vasodilators are useful in patients with chronic heart failure. A combination of arterial dilators and venodilators may be used. Balanced vasodilators are those which act on both the arterial and venous circuits. The converting enzyme inhibitors are examples of balanced vasodilators. Clinical trials have demonstrated that converting enzyme inhibitors alone, and a combination of hydralazine and isosorbide dinitrate both prolong survival in patients with advanced heart failure. Drug tolerance, that is, a diminution of clinical response to a drug on prolonged usage, is the significant problem with vasodilators. Alternating the use of vasodilators or the combined use of two vasodilators may reduce the incidence of tolerance to vasodilators.

Adjunctive therapy The adjunctive therapy includes antiarrhythmic drugs for subjects with severe symptomatic ventricular arrhythmias and the use of anticoagulants in subjects with dilated cardiomyopathy. Cardiac transplantation is an

Table 12.15 Classification of commonly used diuretics in CHF

Class *Drug*	*Site of action*	*Route of administration*	*Total dose in CHF (mg) and frequency*	*Onset (hours)*	*Complications*
A. Thiazides	distal tubule				hyponatremia, hypokalemia
• Hydrochlorthiazide		po	25–200,qd–bid	2	hyperglycemia, pancreatitis
• Chlorothiazide		po, iv	250–750, qd–bid	2	hyperuricemia
• Indapamide		po	2.5–5, qd	2	hypercalcemia, ↑ LDL, metabolic alkalosis (less with indapamide)
B. Pthalimidine derivatives	distal tubule				
• Chlorthalidone		po	25–150, qd	2	as above but hypokalemia may be profound
• Metolazone	distal and proximal tubule	po	2.5–20, qd	1	
C. Loop diuretics	loop of Henle				
• Furosemide		po, iv	20–300, qd–bid	1/2 (iv 5 min)	hyponatremia, hypokalemia metabolic alkalosis, ototoxicity
• Bumetanide		po, iv	0.5–10, qd–bid	1/2 (iv 5 min)	interstitial nephritis
D. Potassium sparing diuretics	distal tubule and collecting duct				hyperkalemia
• Spironolactone		po	25–200, bid	24–48	gynecomastia (spironolactone only)
• Triamterene		po	100–300, qd–bid	48–96	

po= per oral, iv= intravenous, qd=once daily, bid=twice daily, tid= thrice daily

Table 12.16 Classification of commonly used vasodilators in CHF

Class	Drug	Site of action	Route of administration	Dose		Frequency of administration	Frequency of adverse effects	Toxicity
				initial	maintenance			
A. Nitrates								
	• Nitroglycerin	venous	Sublingual, topical, oral or i.v	0.4 mg 0.5–1 inch 2 mg (SR) 5–10 µg/min	 5–15 mg 250–500 µg/min	 tid bid 	 common rare rare	headache, postural hypotension, methemo globinemia
	• Isosorbide dinitrate		sublingual or oral	2.5–10 mg 10–40 mg		q 2 hrs qid	common common	as above as above
B. Calcium channel blockers								
	• Nifedipine	arterial + venous	Oral	10 mg, 20 mg (SR)	10–40 mg	tid bid	rare	pedal edema, postural hypotension
C. Converting enzyme inhibitors								
	• Captopril	arterial + venous	Oral	6.25 mg	12.5–25 mg	tid	rare	hyperkalemia, skin rash, proteinuria, angioedema, cough
	• Enalapril			5 mg	5–10 mg	bid		as above + renal impairment
	• Lisinopril			10–20 mg	20–80 mg	qd		as above

Table 12.16 Classification of commonly used vasodilators in CHF (contd.)

Class	*Drug*	*Site of action*	*Route of administration*	*Dose*		*Frequency of administration*	*Frequency of adverse effects*	*Toxicity*
				initial	*maintenance*			
D. Miscellaneous								
	• Hydralazine	arterial	oral	10–25 mg	25–75 mg	qid	rare	headache, fever, rash, positive ANA
	• Prazosin	arterial + venous	oral	1 mg	1–10 mg	qid	common	first dose hypotension, fluid retention
	• Minoxidil	arterial	oral	2.5–5 mg	5–20 mg	bid	rare	hirsutism, pericardial effusion
	• Nitroprusside	arterial + venous	iv	10–25 µg/min	upto 300 µg/min		rare	thiocyanate toxicity, methemoglobinemia

iv = intravenous, bid=twice daily, tid=thrice daily, qid= four times daily, ANA = antinuclear antibody, SR = sustained release, qd = once daily

alternative therapeutic option in subjects with end-stage cardiac failure refractory to all forms of medical treatment. Left ventricular assist devices and artificial hearts have been used as a bridge to cardiac transplantation in centres outside India.

KEY CONCEPTS

- CHF is a clinical syndrome characterised by the inability of the heart to pump blood commensurate with the metabolic needs of the body. The pathogenetic mechanisms of CHF include a loss of myocardial contractile elements (myocardial infarction, cardiomyopathy), an excessive afterload (force that resists the contraction of the heart; e.g. hypertension, aortic stenosis), and restriction of ventricular filling (reduced ventricular preload, the stretch of the myocardium prior to systole; e.g., mitral stenosis, restrictive cardiomyopathy, constrictive pericarditis).
- CHF may also be classified as systolic failure (the reduced ability to pump in systole) or diastolic failure (reduced ability to fill in diastole). CHF may be a low output condition or, rarely, a high output condition (causes include anemia, thyrotoxicosis, beriberi, Paget's disease of the bone).
- The symptoms of CHF may be due to left ventricular failure (pulmonary congestion resulting in exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea), or due to right ventricular failure (systemic venous congestion resulting in hepatic engorgement, pedal edema). The most common cause of right ventricular failure is left ventricular failure.
- Findings on clinical examination may include tachycardia, a narrow pulse pressure, elevated JVP with a positive abdominojugular reflux, pulmonary rales, cardiac enlargement, a third heart sound, a loud pulmonary component of the second heart sound and murmurs of atrioventricular valve regurgitation.
- The chest X-ray reveals cardiomegaly, and signs of pulmonary venous and arterial hypertension. The ECG may show evidence of an old myocardial infarction or left ventricular hypertrophy.
- An echocardiogram is the key investigation. It identifies valvular heart disease, myocardial disease, prior infarction and left ventricular hypertrophy; it also enables the quantitation of the degree of systolic and diastolic ventricular dysfunction and can identify pericardial disease.
- The management of CHF consists of treating any precipitating cause (anemia, infection, pulmonary embolism, non-compliance with dietary or drug prescription), controlling associated hypertension or diabetes mellitus, abstinence from alcohol, moderate dietary sodium restriction (2 g/day) and drug treatment.
- Diuretics are useful for relieving symptoms of pulmonary congestion. Among the inotropes, digoxin is useful, especially in the presence of concomitant atrial fibrillation. Vasodilators are the most important component of CHF therapy as they prolong survival; nitrates are predominant venodilators, hydralazine is an arterial vasodilator, while the converting enzyme inhibitors are mixed vasodilators. The role of beta-blocking drugs is being investigated. For end stage heart failure, cardiac transplantation is a therapeutic option.

12.5 Congenital heart disease

The incidence of congenital heart disease is approximately 8 per 1000 live births. This section focuses on common congenital heart disease encountered in the adults. Atrial septal defect, ventricular septal defect, patent ductus arteriosis, coarctation of the aorta, pulmonic stenosis, and tetralogy of Fallot comprise almost all of the adult congenital cardiac anomalies.

Atrial Septal Defect (ASD)

ASDs account for approximately 25 per cent of all congenital heart disease seen in the adult. Women have this disorder more often, outnumbering men by a ratio of 3:1.

Classification and embryology Embryologically, atrial septation begins at 5–6 weeks of gestation. The septum primum is a curtain of tissue arising in the cranial portion of the embryonic atrial roof near the midline. It proceeds downwards towards the endocardial cushions, a pair of tissue mounds surrounding the common atrioventricular canal. As the *septum primum* grows towards the endocardial cushions, it leaves a hole on its inferior border called the *ostium primum.* As the septum primum fuses with the endocardial cushions the ostium primum eventually gets obliterated. Shortly before this fusion takes place, an *ostium secundum* appears in the septum primum. The *septum secundum* is a second flap of tissue which arises from the atrial roof to the right of the septum primum. Though the septum secundum grows downwards towards the endocardial cushions it does not fuse with them; instead there is a persistent oval orifice on the inferior border of the septum secundum called the *foramen ovale.* In the first few months after birth, the septum primum and the septum secundum normally fuse with one another to form a single complete interatrial septum. The remnant of the foramen ovale is visible as the *fossa ovalis,* on the right side of the interatrial septum. A patent foramen ovale is not a true defect although under certain circumstances it may function as one. Atrial septal defects are classified as *secundum* (70 per cent), *primum* or partial atrioventricular canal (15 per cent) and *sinus venosus* type (15 per cent). It is important to know the anatomic type of the atrial defect because of important associated anomalies. Roughly, a third of patients with secundum defects have associated mitral valve prolapse and mitral regurgitation. Two-thirds of patients with ostium primum defects have a cleft anterior mitral leaflet, and half the subjects with sinus venosus defects have anomalous drainage of the right-sided pulmonary veins into the right atrium.

Pathophysiology and clinical course Regardless of the type of atrial septal defect, uncomplicated defects result in similar physiologic consequences which vary in magnitude depending on the size of the defect. Blood flow through the atrial septal defect occurs dominantly in diastole in contrast to shunt lesions at other levels. In uncomplicated

atrial septal defect there is a pure right-sided volume overload involving the right atrium, the right ventricle and the pulmonary circulation. The left atrium, the left ventricle and aorta are spared both the pressure and volume overload and are conspicuously normal or even small in size. The magnitude of the shunt is dependent on the relative stiffness of the right and left ventricles (compliance) and the relative pulmonary and systemic vascular resistances. In infants, the right ventricle is stiff and non-compliant so that the left to right interatrial shunting in minimal. As the right ventricular compliance increases (and stiffness decreases) during childhood, left to right interatrial shunting increases as does the pulmonary blood flow. However, young patients with an isolated ASD generally tolerate even large volume shunts well and right ventricular contraction and pulmonary vascular resistance is normal. Older adults suffer from the clinical consequence of the large atrial shunts. Thus pulmonic plethora is associated with pulmonary hypertension and increased pulmonary vascular resistance. The right ventricular volume overload is associated with right heart failure; right atrial volume overload can lead to the loss of sinus rhythm and atrial fibrillation. Severe pulmonary vascular obstruction with right to left shunting (Eisenmenger's physiology) occurs in 5–15 per cent of cases. It is rare before adolescence and common after the age of 50 years. The Eisenmenger syndrome is associated with progressive right heart failure, systemic desaturation (cyanosis), erythrocytosis and risk of paradoxical embolism. When mitral regurgitation complicates a primum or secundum atrial septal defect, it exaggerates the left to right atrial shunting and accelerates the onset of atrial arrhythmias, heart failure and pulmonary hypertension.

Clinical findings The body habitus and facies are normal in patients with ASD. Precordial examination reveals an enlarged hyperdynamic right ventricle and auscultatory evidence of a wide fixed second heart sound. This occurs because an abnormally large quantity of blood enters the right ventricle during both phases of respiration, and the amount of increase in right ventricular blood volume produced by inspiration is comparatively negligible. Therefore, right ventricular systole is prolonged during both inspiration and expiration, thereby explaining the wide, fixed, second heart sound. A grade 2/6 basal systolic ejection murmur is a common finding; it is secondary to an increased flow across the pulmonary valve orifice. In patients with large shunts (pulmonary to systemic flow ratio greater than 2:1), the increased diastolic flow across the tricuspid valve due to the shunt results in a soft mid-diastolic tricuspid flow rumble. A holosystolic murmur heard at the apex and radiating to the axilla indicates associated mitral regurgitation. With severe pulmonary vascular obstruction and shunt reversal, the pulmonic closure sound (P2) becomes loud, the splitting of the second heart sound narrows and the pulmonic systolic flow murmur becomes soft or is absent. Cyanosis, digital clubbing, a high pitched diastolic decrescendo murmur of pulmonary regurgitation, and a right-sided fourth heart sound become prominent.

Investigations The electrocardiogram reveals right axis deviation; right ventricular volume overload is reflected as an incomplete right bundle branch block. Left axis deviation suggests an ostium primum type of defect, or associated mitral regurgitation or myocardial disease. In the primum type of defects, the left axis deviation is secondary to congenital hypoplasia of the anterior radiation of the left bundle branch. The chest X-ray film shows right atrial and right ventricular enlargement, dilatation of the main and proximal pulmonary artery and a normal-looking left heart and aorta. The pulmonary blood flow is increased (plethora) (Fig 12.32). A sinus venosus defect, associated with partial anomalous drainage of a

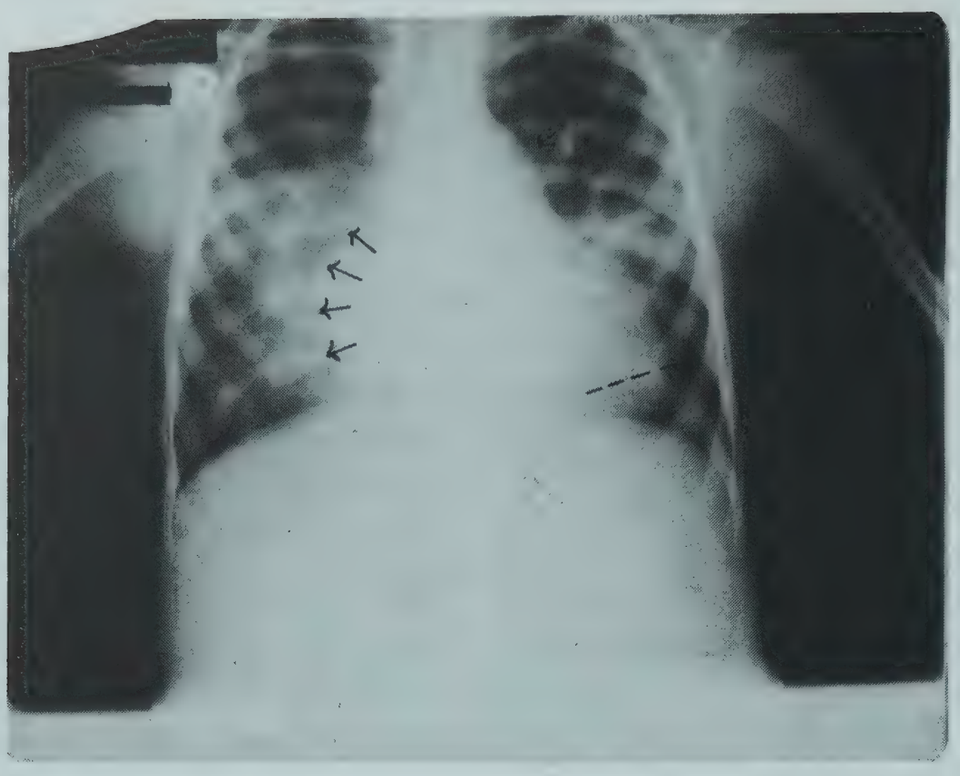


Fig 12.32 Plain X-ray chest (PA view) of a 3-year old boy with repeated chest infection. Note the pulmonary plethora reflecting shunt vascularity, large right atrium (multiple arrows), prominent main pulmonary artery segment (single arrow). There is cardiomegaly and the cardiac apex is turned upwards (dotted arrow) suggesting right ventricular enlargement. This patient had a large fossa ovalis ASD on echocardiographic examination.

right-sided pulmonary vein into the superior vena cava, may demonstrate a dilated superior vena cava on the chest X-ray. Two-dimensional echocardiography and a Doppler study provide definitive diagnosis and permit differentiation of the various types of atrial septal defects. The location of the defect, its size and the presence of secondary effects and complications of the shunt can be seen with the echocardiogram. Right atrial and right ventricular dilatation and a paradoxical motion of the interventricular septum are the hallmark of an atrial septal defect. Doppler and colour flow imaging identify the presence of blood shunting from the left atrium into the right atrium. An estimate of the pulmonary pressure can be provided if tricuspid regurgitation is present. Cardiac catheterisation is not required in most children with typical findings of atrial septal defects and in adults who are less than 40 years of age. If the patient is above 40 years at the time of diagnosis, or has atypical physical findings or associated mitral valve disease, cardiac catheterisation is indicated. A step-up in oxygen saturation in the right atrium on right heart oximetry, and an equalisation of atrial pressures signify a large atrial septal defect.

Management Optimal management of an ASD consists of surgical closure when the shunt ratio (ratio of pulmonary to systemic flow) is more than 2:1. Patients with a shunt ratio lower than this can be followed up medically or treated surgically since the operative mortality is extremely low (less than one per cent). For the best results, surgery should be performed before the school-going age. Closure of the defect in women prior to the child-bearing age is recommended because of the tendency of the patient to delay surgery until family responsibilities have waned and this usually occurs in late middle age when the chances of complications due to an atrial shunt are very high. Patients with pulmonary hypertension with net left to right shunting are usually surgical candidates regardless of the presence of pulmonary hypertension. Patients with net right to left shunting (Eisenmenger syndrome) are

inoperable. Newer modalities of therapy which are still evolving and experimental include transcatheter closure of secundum ASDs using double umbrella-type devices.

Ventricular Septal Defect (VSD)

Ventricular septal defects occur in about 1 in 500 normal births. The incidence of VSDs decreases dramatically during the first year of life as nearly 50 per cent of these defects close. Ultimately, the prevalence of ventricular septal disease in the adult population is about 0.5 per 1000, or 12 per cent of all congenital heart abnormalities seen in adults.

Embryology and anatomy Ventricular septal defects are classified according to the location within the interventricular septum. The interventricular septum is divided into an *inlet* septum, a *trabecular* or muscular septum, a *perimembranous* or subaortic septum and *supracristal* or subpulmonic or outlet septum. The defects which occur in the various components of the ventricular septum go by the respective names. Thus the commonest defects are the perimembranous defects which involve the membranous interventricular septum and are characteristically subaortic in location. They make up more than 75 per cent of all interventricular communications. These defects are in close proximity to the septal leaflet of the tricuspid valve, which in some patients can obliterate or close the defect. The muscular ventricular septum defects account for nearly 10 per cent of all interventricular communications. They may be single or more typically multiple, and on occasion can be so many that the ventricular septum is referred to a *'Swiss cheese' septum*. Defects in the inlet septum constitute the so-called common *atrioventricular canal type* of ventricular septum defects and account for 10 per cent of all ventricular septum defects. They occur in more than 50 per cent of patients with Down syndrome. These defects occupy the inlet portion of the ventricular septum beneath the tricuspid valve, extending from the region of the junction of the anuli of the mitral and tricuspid valve posteriorly to the membranous septum anteriorly. Deficiency or clefts in the mitral and tricuspid leaflets are common as also are abnormal attachment of the chordae tendineae. Supracristal ventricular septal defects are uncommon; they account for 5 per cent of interventricular communications.

The supracristal VSD is located above and anterior to the crista supraventricularis, just beneath the aortic anulus. The clinical location of the supracristal defect can leave the aortic anulus without support beneath the right coronary leaflet cusp, thereby encouraging progressive prolapse of the right aortic valve cusp and consequent aortic regurgitation. Significant aortic regurgitation is rare before the age of two years, increases in frequency by adolescence, eventually occurring in 6–10 per cent of adults with this type of a VSD.

Pathophysiology and clinical course Ventricular septal defects are systolic shunts and therefore, the right ventricle is subjected to both a pressure and a volume overload. The increased flow to the right side of the heart is carried to the pulmonary circulation and thereafter reaches the left atrium, causing left atrial and left ventricular volume overload. Increased pulmonary blood flow can lead to increased pulmonary vascular resistance and increased pulmonary arterial pressures. The hemodynamic consequences of a VSD are determined largely by the size of the defect, the ratio of the pulmonary and systemic vascular resistance, and the presence of associated lesions. Small defects are less than 0.5 cm^2, moderate sized defects are 0.5 to 1 cm^2 (smaller than the diameter of the aortic anulus), and larger defects are greater than 1 cm^2. Small defects do not alter cardiac function or elevate pulmonary artery pressures. However, because of the large interventricular pressure gradient across these defects, they cause the loudest of all VSD murmurs. These

defects have the greatest tendency to close spontaneously. Because of a jet lesion on the right ventricular endocardium, these small VSDs can serve as foci for infective endocarditis. Large defects are associated with right ventricular, left atrial and left ventricular enlargement along with elevated pulmonary arterial pressures. The increased pulmonary vascular resistance creates a progressive pressure overload on the right ventricle and ultimately results in reversal of the direction of the interventricular shunt with right to left shunting being the predominant direction. This situation is called the Eisemenger's complex. Sometimes even large ventricular septal defects can diminish in size and close spontaneously. Occasionally the magnitude of the shunt may diminish due to secondary hypertrophy of the musculature of the right ventricular outflow tract (infundibular hypertrophy). This phenomenon occurs in 5 per cent of all VSDs.

Clinical findings The body habitus and facies of these patients are usually normal except for those with Down syndrome. Patients with ventricular septal defect have a systolic thrill at the left sternal border, an enlarged hyperdynamic apical impulse, and a loud pansystolic murmur heard best at the left sternal border in expiration on precordial examination. The murmur begins with S1 and ends with S2, and is loudest in smaller size defects. In patients where the pulmonary to systemic flow ratio is more than 2:1, the increased return of pulmonary venous blood to the left atrium causes increased diastolic flow across the mitral valve and produces a mid-diastolic rumble across the mitral valve. The increased volume of blood flowing into the right ventricle accounts for a wide and 'variably' split second heart sound. As pulmonary vascular obstruction develops, the murmur diminishes in duration (frequently becoming ejection in quality), the pulmonary closure sound is loud, and a right ventricular impulse may become palpable. As pulmonary vascular obstruction progresses further, the ejection murmur may disappear and the second heart sound may be normally split with a very loud pulmonic component. A high-pitched diastolic decrescendo murmur of pulmonary regurgitation may make its appearance at this stage. Eventually, with dominant right to left shunting, systemic desaturation and clinical cyanosis develop and signs of right ventricular failure with tricuspid regurgitation may be found.

Investigations The electrocardiogram is of value in assessing the patient with VSD. The ECG is normal in small VSDs. With larger VSDs, there may be evidence of both left atrial and left ventricular enlargement along with a right ventricular conduction defect. A prolongation of the PR interval is common in patients with a common atrioventricular canal type of defect. The QRS axis is usually normal in patients with uncomplicated VSDs. The presence of right axis deviation along with evidence of right ventricular hypertrophy may indicate either pulmonary vascular obstruction with Eisenmenger syndrome, or progressive infundibular obstruction and right ventricular pressure overload. Marked left axis deviation would suggest a common atrioventricular type of ventricular septal defect. The chest X-ray film is normal in patients with a small VSD. With larger size defects, characteristically there is increased pulmonary blood flow, and left atrial, and left ventricular enlargement are prominent. The aorta is normal or small in size. As pulmonary arterial hypertension develops, there may be marked proximal pulmonary artery dilatation at the hilum and peripheral vascular pruning in the lung fields. Two-dimensional echocardiography and Doppler examination help in delineating the location of the defect, the number of defects, the presence of associated chamber enlargement and associated cardiac defects. Doppler echocardiography is also useful in documenting the presence of associated pulmonary arterial

hypertension, right ventricular infundibular obstruction and aortic valve prolapse with aortic regurgitation. Cardiac catheterisation is not required in an asymptomatic patient with a small VSD and a normal-sized heart on chest X-ray and a normal ECG. In subjects with a pulmonary-to-systemic flow ratio more than 2:1, surgical intervention is essential and cardiac catheterisation may be necessary. The objectives of cardiac catheterisation are to assess the size of the left to right shunt, measure the pulmonary artery pressure and pulmonary vascular resistance and to assess the reversibility of the elevated pulmonary vascular resistance. In those without elevated pulmonary vascular resistance corrective surgery consists of either suture or patch closure of the VSD. Patients with significant infundibular obstruction also require infundibulectomy. Patients with Eisenmenger syndrome are inoperable. The optimal age of repair is before the child reaches the school-going age. Surgical risks are substantially higher with multiple 'Swiss cheese' type VSDs and with straddling of the AV valves across the VSD. In these patients pulmonary artery banding is the preferred early palliative approach in infancy, with the possibility of definitive repair and debanding after several years.

Patent Ductus Arteriosus

Patent ductus arteriosus (PDA) is an obligatory component of the normal fetal circulation, serving as a right to left shunt, providing much of the prenatal blood flow to the descending thoracic aorta. Persistent patency beyond the early weeks of life, however, is abnormal. PDA is present in 10 per cent of adults with congenital heart disease. There is an association with infants whose mothers have had rubella infection in the first trimester of pregnancy, in prematurely born infants and in infants born at high altitudes. In predilection females outnumber males in a ratio of 2:1.

Anatomy and embryology The ductus arteriosus of the fetus extends from the aortic isthmus, that is, just distal to the origin of the left subclavian artery, to the left pulmonary artery just distal to the pulmonary artery bifurcation. It is thin-walled and tapers towards the end adjoining the pulmonary artery. After birth, it contracts and remains as the *ligamentum arteriosum.*

Pathophysiology and clinical course The physiologic consequences of PDA depend on its cross-sectional area, and the pulmonary artery vascular resistance as compared to the systemic vascular resistance. Large PDAs allow a large volume of blood to flow into the pulmonary circuit with increased pulmonary artery pressure, increased left atrial venous return and left ventricular volume overload. Patients with a small PDA are asymptomatic. Patients with a large ductus have symptoms and findings of heart failure, and occasionally pulmonary vascular obstruction (Eisemenger syndrome). Infective endocarditis is a complication that typically occurs on the pulmonary side of the ductus and may occur regardless of the size of the PDA. Aneurysmal dilatation of the PDA with calcification, dissection, or rupture is rare but is seen occasionally in both infants and adults, especially the elderly.

Clinical findings The facies and body habitus are normal except in patients with the congenital rubella syndrome. The latter have cataract, appear retarded and may be deaf. The characteristic physical finding is the PDA murmur (*Gibson murmur*) heard best at the left upper sternal region on the left infraclavicular area. The murmur is high-pitched, begins with the first heart sound, peaks at the second heart sound and extends beyond the second heart sound for a variable interval into diastole. The murmur typically has multiple clicks, has a machinery quality and may obscure the heart sounds in the infraclavicular region. With tachycardia or with pulmonary vascular obstructive disease, the duration of the diastolic

murmur decreases. With pulmonary vascular obstructive disease, the diastolic component may disappear and the pulmonic closure sound increases in intensity, leaving only a predominant systolic murmur. With further increase in pulmonary vascular resistance, the findings may include a loud pulmonic component of the second heart sound and no murmur may be heard. The lower extremities then receive the desaturated pulmonary artery blood flow (with right-to-left shunting) and cyanosis and clubbing of the toes may be seen (*differential cyanosis*).

Investigations The electrocardiographic findings correlate with the size of the ductus. With a small ductus, the ECG is normal. A large PDA produces left atrial and left ventricular enlargement. With the development of pulmonary vascular obstructive disease, right atrial enlargement and right ventricular hypertrophy may become manifest on the ECG. The cardiac rhythm, conduction, and the QRS axis are normal. The chest X-ray film may be normal in patients with a small PDA. With a large ductus, the findings include pulmonary plethora, enlargement of the left atrium and the left ventricle, and dilatation of the proximal pulmonary arteries and of the ascending aorta. A prominent aortic knob shadow distinguishes a PDA from intracardiac shunts (ASDs and VSDs) in which the aortic knob is small. Calcification of the PDA may be visible in elderly adults, particularly those with pulmonary hypertension. Two-dimensional and Doppler echocardiography allow direct imaging of the ductus and visualisation of the ductus flow. The Doppler study allows assessment of the shunt magnitude and may provide an estimate of pulmonary arterial pressure. A small ductus may be visualised only on colour-coded Doppler flow mapping. Cardiac catheterisation may not be essential in the young patient with typical clinical and non-invasive findings. It may be required when the findings are atypical, and in the older patients for the assessment of coronary anatomy. Right heart catheterisation reveals a significant oxygen step-up at the level of the pulmonary artery and the catheter may enter the ductus from the pulmonary artery and then enter the descending thoracic aorta.

Treatment In children all patent ducts should be closed. The therapeutic procedure of choice is double ligation of the ductus, with or without division, performed through a left posterior thoracostomy in an operation that does not require heart-lung bypass. The optimal age for an elective ligation is one year. It is not clear whether the asymptomatic young adult with a small PDA and normal heart size and normal pulmonary artery pressure must be subjected to duct closure. Prophylaxis for infective endocarditis and a close interim observation is an acceptable therapeutic alternative. Newer methods for treating small PDAs include transcatheter closure of the PDA with Teflon plugs or double umbrella prostheses. These devices, however, remain experimental at present.

Coarctation of the Aorta

Coarctation of the aorta accounts for 15 per cent of congenital heart abnormalities in adults, with men outnumbering women in a ratio of 2:1. Coarctation is more common in patients with Turner syndrome. It is a treatable form of hypertension, readily evident in a careful physical examination.

Pathophysiology and clinical course Coarctation is a fibrous narrowing of the aortic lumen in the region of insertion of the ductus arteriosus. It may vary in morphology from being a discrete diaphragm-like infolding of the aortic wall, to a narrowing of the aortic isthmus without a discrete shelf. Physiologically, coarctation of the aorta causes obstruction to the left ventricular outflow. This obstruction causes hypertension in the proximal aorta and the left ventricle. Hypertension is largely systolic;

elevation of mean aortic pressure occurs, though to a lesser extent. Perfusion distal to the coarctation is maintained through collateral channels which are more extensive in those patients with a severe degree of obstruction. Distal to the coarctation, systolic blood pressure is characteristically diminished and the systolic upstroke of the pulse is delayed. The mechanisms by which coarctation causes hypertension is not entirely clear; a reduced carotid baroreceptor sensitivity, mechanical factors related to the obstruction and activation of the renin and angiotensin systems are some of the proposed mechanisms. Concentric left ventricular hypertrophy develops and in late adult life there may be ventricular dilatation and ventricular failure. Symptoms of lower extremity ischemia may develop and are related to the diminished blood flow to the lower half of the body. A bicuspid aortic valve may be found in 25–33 per cent of patients with coarctation of the aorta. Symptoms due to the coarctation in children are secondary to hypertension and include headache, epistaxis, bounding carotid pulsation, and uncommonly intermittent claudication. Heart failure has a bimodal distribution, with an early peak in infancy related by and large to associated cardiac anomalies like PDA, VSD or aortic stenosis. The second peak occurs in the fourth decade and is related to valvular stenosis, myocardial disease or coronary artery disease. About 5–10 per cent of patients may have a cerebrovascular accident which may be related to chronic hypertension or may be associated with a congenital berry aneurysm of the circle of Willis. Infective endocarditis is a complication occurring in 2–5 per cent of patients and may involve the site of coarctation or associated lesions like a bicuspid aortic valve. Severe hypertension and toxemia, are common in pregnant women and have a significant risk of aortic dissection.

Clinical findings The body habitus and facies are usually normal though some patients may have underdeveloped lower extremities as compared to the well-developed upper extremities and the upper body. Patients with Turner syndrome have a short stature, a webbed neck and nipples set wide apart. Upper extremity hypertension is present and upper extremity pulses are more forceful than lower extremity pulses which are weak and delayed or occasionally absent. Patients with extensive collaterals may have normal lower extremity pulses, but careful comparison with carotid or brachial pulses may still reveal a relative difference. Superficial scapular collaterals may be palpated beneath the skin over the back on careful examination. Examination of the cardiovascular system reveals prominent suprasternal pulsations, systolic thrill and forceful sustained left ventricular cardiac apex. A fourth heart sound and an ejection sound may be present. A systolic murmur may be heard over the left upper back (related to the coarctation site), and continuous murmurs related to extensive collateral flow may be heard over the back.

Investigations The ECG is normal in children but may reveal left ventricular hypertrophy and left atrial enlargement in adults. The presence of significant left ventricular hypertrophy in infants suggests associated left ventricular outflow tract obstruction. The frontal plain QRS axis, the conduction system and rhythm are normal. A right ventricular conduction defect may be seen in children. The plain chest X-ray film reveals a normal heart size and the typical '*figure three*' *sign* which refers to a dilated left subclavian artery above, the indentation secondary to the coarctation, and the poststenotic aortic dilation below. The ascending aorta is dilated and rib-notching may be evident in adolescents and older children, being best seen along the under surface of the third to fifth ribs. Two-dimensional echocardiography and a Doppler study provide confirmation of the diagnosis. Visualisation of the coarctation is based on

examination from the suprasternal notch. Doppler ultrasound also helps to localise the site and assess the pressure gradient across the obstruction. Cardiac catheterisation or digital subtraction angiography are studies which reveal the extent of the coarctation, the anatomy of the arch and the presence of collateral vessels.

Treatment Both percutaneous balloon angioplasty of the coarctation site and surgery of the coarctation site (consisting of coarctectomy and reanastomosis) constitute valid therapeutic options for the treatment of the coarctation of the aorta. Elective repair or balloon dilatation of uncomplicated asymptomatic subjects, should be performed when the patient is between the ages of three and five years as the operative risk is low and the incidence of late, postoperation hypertension is minimal. Balloon angioplasty is also the procedure of choice for dilating residual stenosis or restenosis, that is, after early surgical repair. However, balloon dilatation carries some risk of late aneurysm formation at the site of the coarctation. Important perioperative complications include the increased risk for intraoperative spinal cord ischemia, especially in patients with mild coarctation and few collaterals. *Paradoxical hypertension* occurring in the postoperative phase is another important complication which needs prompt identification and treatment to avoid sequelae that may include bowel necrosis and mesenteric arteritis. Chemoprophylaxis against endocarditis in infants should be a lifetime measure regardless of prior repair. Late postoperative complications include persistent postoperative hypertension, especially in patients in whom it is corrected after the age of six years. Stroke and aortic dissection continue to be postoperative risks although they are less likely to occur than in unoperated patients.

Pulmonic Stenosis

Congenital pulmonary stenosis accounts for 10 per cent of congenital heart abnormalities in adults.

Pathophysiology and clinical course In the majority of patients, pulmonary stenosis is valvular and secondary to a partially fused tricuspid or less commonly, a bicuspid pulmonic valve. Poststenotic dilatation of the pulmonary artery and the left pulmonary artery is characteristic of valvular pulmonic stenosis. This abnormality imposes a chronic pressure overload on the right ventricle that undergoes compensatory hypertrophy. Sometimes there is selective hypertrophy of the infundibulum beneath the pulmonic valve which also contributes to the overall right ventricular outflow tract obstruction. In mild pulmonic stenosis, right ventricular systolic pressure is less than 50 per cent of systemic pressure, being less than 50 mmHg. Moderate pulmonic stenosis is defined by a right ventricular systolic pressure ranging from 50–75 per cent of systemic pressure (absolute 50–75 mmHg). Severe pulmonic stenosis is defined by a right ventricular systolic pressure greater than 75 per cent of systemic pressure (absolute > 75 mmHg). Patients with mild and moderate pulmonic stenosis have few or no symptoms. Severe pulmonic stenosis may cause fatigue and dyspnea in children and adults. Overt heart failure is uncommon in the fourth and fifth decades. Chest pain may occur in adults with severe right ventricular hypertrophy and may be secondary to excessive circulatory demands on the hypertrophied right ventricle. Infective endocarditis has been reported in 1–2 per cent of patients.

Clinical findings The body habitus and facies are usually normal except in those with congenital rubella syndrome or the Noonan syndrome. The latter is characterised by small stature, mental retardation, *micrognathia, hypertelorism,* undescended testes and skeletal abnormalities. Physical findings on auscultation vary with the severity of valvular obstruction. With severe pulmonic stenosis, a prominent jugular venous A wave is seen and there is a

thrill at the upper left sternal border and a palpable right ventricular impulse is present. An ejection sound is heard in the pulmonic area and is unique among right heart auscultatory findings in that it is louder during expiration. The interval between the ejection sound and the first heart sound correlates inversely with the severity of pulmonic stenosis, being longer in milder stenosis and shorter in severe pulmonic stenosis. The intensity, duration and contour of this murmur are helpful in assessing the severity of pulmonic stenosis. The murmur is ejection in quality and loudest at the upper left sternum. In mild pulmonic stenosis, the murmur is softer and shorter and peaks early in contrast to the long, loud and late peaking murmur of severe pulmonic stenosis.

Investigations The ECG is normal in patients with mild pulmonic stenosis; right atrial and right ventricular hypertrophy, and right axis deviation may be seen in patients with moderate and severe pulmonic stenosis. The height of the right precordial R wave correlates well with the systolic right ventricular pressure. The chest X-ray film may be normal in patients with mild pulmonic stenosis. Patients with moderate or severe pulmonic stenosis have right ventricular and right atrial enlargement along with the characteristic poststenotic dilatation of the main and left pulmonary arteries. Two-dimensional echocardiography and Doppler study are valuable for evaluating the presence, the level and the severity of pulmonary stenosis. The stenotic valve is readily visualised as thick and typically doming in systole. Doppler echocardiography allows for accurate estimation of the overall outflow tract pressure gradient. Cardiac catheterisation is not required in patients with mild pulmonic stenosis; it may be required in patients with moderate or severe stenosis before surgical or balloon interventions. For children and adults with moderate or severe valvular pulmonic stenosis, percutaneous balloon pulmonary valvuloplasty offers results comparable to surgical valvotomy. In fact, percutaneous balloon valvuloplasty is regarded by several physicians as the ideal treatment for valvular pulmonic stenosis; it provides excellent relief of obstruction with minimal risk and an excellent long term prognosis on follow-up. Pulmonary valve incompetence is common both after balloon valvuloplasty as well as after surgical valvotomy, but is generally tolerated well. Chemoprophylaxis against endocarditis is, however, still indicated for patients who have undergone balloon or surgical valvotomy.

Tetralogy of Fallot

By definition this anomaly is characterised by four anatomic components:

1. a ventricular septal defect that is typically large and membranous in location;
2. right ventricular outflow tract obstruction that is both infundibular and valvular (both of varying severity);
3. an aorta that overrides the ventricular septal defect; and
4. a hypertrophied right ventricle secondary to chronic pressure overload.

Of these, the first two components are of primary physiologic importance.

Epidemiology The disorder accounts for about 10 per cent of congenital heart disease in adults, and for 50 per cent of cyanotic heart disease in adults. A 3–5 per cent incidence has been reported in the siblings and offspring of patients with tetralogy of Fallot.

Pathophysiology and clinical course Only the first two components of the tetrad listed above are of primary physiologic importance. The right ventricular obstruction is typically fibromuscular and infundibular (but may be valvular or a combination) and decreases pulmonary blood flow. The VSD is typically subaorticand allows right to left shunting of blood that leads to systemic desaturation of a variable degree.

The clinical course is characterised by cyanosis from early infancy with episodic worsening, known as cyanotic spells; spells are especially common in the first two years of life before the development of protective natural systemic circulation to pulmonary circulation collaterals. The episodes are precipitated by exertion, warm weather, dehydration and are characterised by deepening cyanosis irritability, hyperventilation and sometimes syncope and seizures. The occurrence of spells diminishes after two years but the risk of cerebral abscess formation increases thereafter. Thrombotic strokes may occur being related to increased blood viscosity resulting from erythrocytosis or *paradoxical embolism,* that is, right-sided thrombus reaching left-sided circulation due to right to left shunting across the VSD. Bacterial endocarditis is an additional complication, and may affect the pulmonic valve or the overriding aortic valve.

Squatting is an exclusive behaviour of patients with this disease. Squatting increases systemic vascular resistance and favours greater blood flow to the lungs which in turn improves systemic oxygen saturation.

Clinical findings Digital cyanosis and clubbing are salient clinical features. Cardiac auscultation reveals a normal first heart sound and a single loud second sound that represents aortic closure; the pulmonary closure is inaudible. An ejection sound is typical and arises from the overriding aortic valve and dilated aorta. A systolic ejection murmur at the upper left sternum is also a typical finding, the intensity of murmur being inversely related to the severity of pulmonic obstruction. Thus, milder right ventricular obstruction is associated with a loud and long murmur and severe obstruction produces a short, soft murmur or even no murmur.

Investigations The ECG reveals right axis deviation and right ventricular hypertrophy. The chest X-ray reveals a normal sized heart with a boot-shaped contour (*couer en sabot*). This shape is due to a concave upper left cardiac border (secondary to a small main pulmonary artery), and a prominent upturned lower left cardiac border (secondary to right ventricular hypertrophy) (Fig 12.33). A right-sided aortic arch (which indents the right margin of the trachea) is

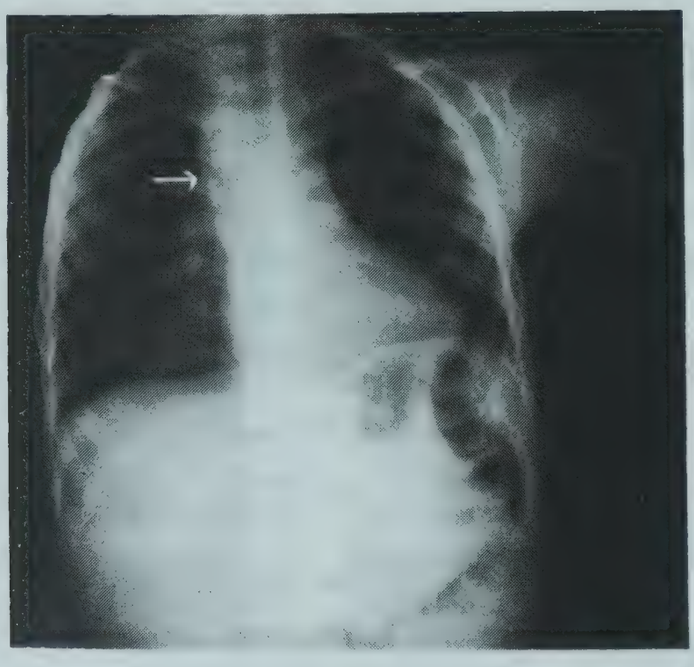


Fig 12.33 Plain X-ray chest (PA view) of a 5-year old boy with Fallot's tetralogy. The cardiac silhouette is boot-shaped (couer en sabot). Note the decreased pulmonary vasculature (oligemia) and the right-sided aortic arch (marked by arrow)

seen in 25 per cent of patients. Two-dimensional echocardiography delineates the morphology of the pulmonary arteries and their confluence and the location and number of VSDs. Cardiac catheterisation is required to assess the pulmonary arteries and right ventricular outflow tract anatomy, to exclude multiple VSDs and for assessment of the coronary artery origin.

Management Surgery for tetralogy of Fallot may be palliative or definitive. Palliative procedures involve the creation of a shunt between the systemic and pulmonary circulation so as to increase pulmonary blood flow and decrease systemic arterial desaturation. One such favoured procedure involves anastomosis of the subclavian artery to the ipsilateral pulmonary artery (Blalock-Taussig shunt). These procedures are used primarily in patients with an anatomy unfavourable for definitive repair. Definitive repair consists of patch closure of the VSD, and relief of right ventricular obstruction (which may require the use of a patch).

KEY CONCEPTS

Atrial septal defect

- An ASD may be of the secundum type (involving the fossa ovalis), primum type (A-V canal defect), or of the sinus venosus type (high septum, often associated with partial anomalous pulmonary venous drainage).
- ASDs result in right atrial and right ventricular volume overload. Pulmonary hypertension may develop.
- Clinical presentation is with repeated chest infection in children and with atrial arrhythmias in adults. Physical examination findings include a wide and fixed S_2, ejection systolic flow murmur across the pulmonary valve, and a mid-diastolic flow murmur across the tricuspid valve (if the shunt is large, i.e., $Q_P:Q_S \geq 2:1$).
- The ECG shows right axis deviation and an incomplete right bundle branch block pattern. The presence of left axis deviation suggests an A-V canal type of defect or associated MVP with mitral regurgitation. The chest X-ray shows increased pulmonary blood flow, and RA and RV enlargement. The echocardiogram is diagnostic: it identifies the location of the defect and any associated anomalies, helps quantitate the magnitude of the shunt and associated pulmonary hypertension.
- The treatment includes anti-CHF measures, and surgical closure for large defects.

Ventricular septal defect

- VSD is the most common congenital heart defect. A VSD may be a defect in the membranous (perimembranous VSD), muscular (swiss-cheese septum), or the outflow (supracristal) septum.
- A significant proportion of VSDs close by the age of 1 year. Large defects cause right ventricular and left atrial volume overload and pulmonary hypertension. As a result congestive heart failure may occur in infancy. Increased pulmonary flow is associated with repeated chest infections. Pulmonary hypertension is initially reversible. Severe irreversible pulmonary hypertension (Eisenmenger syndrome) results in right to left shunting and cyanosis; this condition is associated with very high mortality. Other potential compli-cations of a VSD include endocarditis and aortic regurgitation.
- Clinical features include a systolic thrill, a loud pansystolic murmur at the lower left sternal border, and a wide variable split S_2 with an accentuated P_2. Large shunts ($Q_P:Q_S \geq 2:1$) are associated with a mid-diastolic flow murmur across the mitral valve.
- The ECG shows evidence of LA overload and, later, of RVH. The X-ray shows cardiomegaly, dilatation of the MPA, pulmonary plethora and left atrial enlargement. The echocardiogram is diagnostic; it can localise and quantitate the shunt, assess the degree of pulmonary hypertension and evaluate for the presence of associated anomalies (such as PDA or aortic coarctation). Cardiac catheterisation confirms step-up at the right ventricular level on oximetry.
- The treatment consists of anti-CHF measures, endocarditis prophylaxis, and treatment of intercurrent infections. Surgical closure is recommended for large defects.

Patent ductus arteriosus

- A PDA results in blood flow from the aorta into the pulmonary artery usually distal to take off of the left subclavian artery. It results in LA and LV volume overload.

- ➢ The clinical presentation is with CHF in infancy and repeated chest infection. A small PDA may be asymptomatic. There is an increased risk of endarteritis.
- ➢ The physical finding of a continuous machinery murmur with multiple clicks is pathognomonic of a PDA. The pulse pressure is wide and the pulse is bounding.
- ➢ The ECG shows evidence of LA and LV volume overload. The chest X-ray shows increased pulmonary blood flow and a prominent ascending aortic shadow. A PDA in a middle-aged adult may appear calcified.
- ➢ Surgical closure is recommended for a PDA if $Q_P : Q_S \geq 2:1$.
- ➢ Endocarditis prophylaxis is advised.

Coarctation of the aorta

- ➢ A coarctation is a localised medial shelf which is distal to the left subclavian artery at or near the insertion of the ductus arteriosus. This results in increased mechanical resistance to left ventricular ejection. Systemic hypertension results because of this mechanical obstruction, baroreceptor resetting and activation of the renin-angiotensin system. Coarctation of the aorta may be associated with a congenital bicuspid aortic valve or a congenital intracranial berry aneurysm.
- ➢ The clinical presentation is with CHF in infancy and with asymptomatic hypertension in young children and adolescents. Endarteritis is a potential complication. Clinical symptoms include leg fatigue and intermittent claudication. Findings on clinical examination include diminished and delayed femoral pulses (brachio-femoral delay), increased blood pressure in the upper extremities, continuous murmurs over the back (due to flow in the collaterals) and palpable collaterals.
- ➢ The ECG finding is LVH. The chest X-ray findings include notching of the ribs, and the figure 3 sign (pre- and poststenotic dilatation of the descending thoracic aoftic segment near the coarctation). Echocardiography is useful in confirming the diagnosis (suprasternal view) and estimating the gradient across the obstruction (Doppler).
- ➢ The treatment consists of control of hypertension and relief of the mechanical obstruction with either balloon angioplasty or surgery.

Tetralogy of Fallot

- ➢ The basic abnormality in TOF is a malalignment of the infundibular septum; this results in the tetrad of a VSD (perimembranous), an overriding aorta, infundibular pulmonic stenosis and right ventricular hypertrophy. There may be an associated right-sided aortic arch.
- ➢ The clinical spectrum varies from severe cyanosis at birth to mild cyanosis. There may be a history of hypercyanotic spells that are relieved in part by squatting (increased peripheral resistance with a resultant reduction in right to left shunt and increase in pulmonary flow).
- ➢ The findings on cardiac examination include a single S_2 and a pulmonary ejection systolic murmur (across an obstructed RVOT).
- ➢ The ECG shows right axis deviation and right ventricular hypertrophy. The chest X-ray shows a boot-shaped heart (couer en sabot; small heart, concave pulmonary artery segment and reduced pulmonary blood flow).
- ➢ Cyanotic spells are treated by placing the child in a knee chest position, and administering supplemental oxygen, intravenous morphine, a beta-blocker (propranolol) and methoxamine. Definitive treatment is total surgical correction. If the pulmonary arteries are small in size, a palliative Blalock-Taussig shunt may be performed initially.

12.6 Ischemic heart disease

Atherosclerosis and Coronary Risk Factors

Atherosclerosis is the condition in which the inner layers of the arterial walls become thick and irregular because of fatty deposits mainly of cholesterol.

Pathology Atherosclerotic lesions are commonly classified as one of three types:

1. fatty streaks,
2. fibrous plaques, and
3. complicated lesions.

The earliest lesions of atherosclerosis are the *fatty streaks*. The fatty streaks are universal in all children and begin in the aorta as early as in infancy. The fatty streaks contain about 25 per cent lipid and are usually sessile and non-obstructive. A relationship between fatty streaks and subsequent fibrous plaques is presumptive. Fatty streaks are also found in the coronary arteries, usually in the third and fourth decade. The *fibrous plaques* consist of raised lesions of the arterial intima and represent the most characteristic lesion of atherosclerosis. Unlike the fatty streaks which are ubiquitous, fibrous plaques occur in subjects with advanced atherosclerosis. The fibrous plaques consist of a central core of extracellular lipid covered by a fibromuscular cap of smooth muscle cells, macrophages, and collagen. The *complicated lesion* of atherosclerosis represents a calcified fibrous plaque with superimposed necrosis, ulceration and/or thrombosis. The complicated lesions are frequently associated with acute symptoms.

Different parts of the arterial tree vary in their susceptibility to atherosclerosis and this leads to a non-uniform distribution of lesions. The aorta, especially its abdominal part below the renal arteries, is more severely affected by atherosclerotic lesions. The arteries of the lower limbs are more frequently involved by atherosclerosis than those of the upper limbs. In the coronary arteries, atherosclerosis is nearly always found in the epicardial portions of the vessels. In the cervical and cerebral arteries, atherosclerosis first appears at the base of the brain, in the carotid, basilar and vertebral arteries, with a predilection for the proximal portion of the internal carotid artery in the neck.

Pathogenesis The most widely accepted theory for the pathogenesis of atherosclerosis is referred to as the '*response to injury*' hypothesis. According to this hypothesis, repetitive injury of the endothelium which may be subtle or gross, results in the loss of endothelial cell function. Examples of such injuries may be the mechanical injury due to hypertension, or chemical injury due to chronic hypercholesterolemia. Endothelial cell dysfunction culminates in loss of integrity of the endothelium with exposure of the subendothelial tissue to increased concentrations of blood constituents. Blood platelets adhere and aggregate and form microthrombi at the sites of endothelial injury and release various granular components, including a potent mitogenic factor called *platelet derived growth factor*. This stimulates the

migration of medial smooth muscle cells into the intima and their proliferation at these sites of injury. Blood-borne monocytes also adhere to the endothelial cells and migrate into the arterial wall to become resident macrophages. Thus, a slowly progressive lesion of atherosclerosis evolves with an increase in smooth muscle cells, macrophages, connective tissue and lipids. Further progression of atherosclerosis occurs with repetitive damage to the fibrous plaques (complicated plaque formation). When a fibrous plaque undergoes further injury or ruptures or ulcerates, components of the vascular medial layer, particularly the fibrous collagen, are exposed. This results in marked platelet aggregation with formation of a mural thrombus over the ruptured or ulcerated plaque. The resulting thrombus may be non-occlusive or occlusive. Recurrent episodes of plaque rupture and superimposed thrombosis and organisation result in *intraluminal thrombosis* which is dynamic and repetitive and results in the common acute coronary syndromes such as unstable angina, acute myocardial infarction and sudden cardiac death (explained later). Atherosclerosis of the coronary arteries is referred to as coronary heart disease or ischemic heart disease.

Epidemiology Ischemic heart disease is the major single cause of premature cardiovascular death in most industrialised countries in Europe and America. There is a trend towards increasing morbidity and mortality due to ischemic heart disease in the developing countries too. Ischemic heart disease is more common in males, females being relatively spared during the premenopausal years. Epidemiologic studies have identified certain conditions as risk factors for ischemic heart disease as these conditions bear a causative relation to the disease. A few of these factors are irreversible whereas others are reversible. Thus, among the various risk factors for coronary atherosclerosis, age (more than 65 years), gender (male sex), and genetic factors (family history of premature ischemic heart disease, that is, before the age of 55 years in a parent or sibling) are considered to be irreversible risk factors. The reversible risk factors include hyperlipidemia, smoking, hypertension, diabetes mellitus and severe obesity. Hyperlipidemia results in elevated circulating levels of lipoproteins which results in a greater likelihood of lipids gaining entrance to the arterial wall at the sites of endothelial injury. Once the lipoproteins enter the wall of the arteries, they are modified chemically into oxidised lipoproteins which gain access into the scavenger macrophages inside the arterial walls. The macrophages are converted into foam cells. Hypertension enhances atherosclerosis by causing mechanical stress and the consequent injury of endothelial cells, especially at specific high pressure sites within the arterial tree. Similarly, smoking also causes repetitive chemical injury to the endothelial cells (related to hypoxemia and high levels of carboxyhemoglobin). Diabetes mellitus provides a unique milieu wherein metabolic abnormalities result in accelerated atherosclerosis, partly related to defective endothelial cell function and partly to platelet dysfunction. Obesity (more than 30 per cent overweight) is strongly associated with increased cholesterol levels. Obesity is also associated with other coronary risk factors such as hypertension, hyperlipidemia and hyperglycemia.

Independent of these associated risk factors adiposity produces insulin resistance in peripheral tissues, that is, in the muscles and in the adipose tissue. This results in compensatory hyperinsulinemia and the enhanced production of triglyceride-rich lipoproteins. Hyperinsulinemia may directly affect arterial wall metabolism; there is increased endogenous lipid synthesis by the arterial wall and a stimulus to the proliferation of arterial smooth muscle cells.

Table 12.17 lists the risk factors for coronary atherosclerosis.

Table 12.17 Risk factors for coronary artery disease

Non-modifiable	*Modifiable*	
	Strong evidence	*Suggestive evidence*
Age	Hypertension	Obesity
Male sex	Hyperlipidemia	Stress
Family history of coronary disease	Smoking	Left ventricular hypertrophy
	Physical inactivity	Hyperhomocysteinemia
	Diabetes mellitus	Elevated lipoprotein A

Lipid and Lipoprotein Metabolism – Hyperlipidemia

Normal cholesterol metabolism

Cholesterol is a multicyclic nuclear compound of the steroid family and is an essential part of the cell membranes, the D-vitamins and of adrenal steroids. In humans, cholesterol synthesis occurs chiefly in the liver and the intestine. Plasma cholesterol concentrations are tightly regulated by removal processes keyed to specific liver and extrahepatic cell receptors. Cholesterol is seen only in animal fat, it is not found in plants. Triglycerides, on the other hand, are storage forms of energy consisting of long chain fatty acids which are attached to a glycerol backbone. These fatty acids are water-insoluble long chain hydrocarbons that may or may not have double bonds within the chain. Saturated fatty acids have no double bonds in the chain and unsaturated fatty acids have one or more double bonds within the hydrocarbon chain. Monounsaturated fatty acids have one double bond within the hydrocarbon chain. Lipids are vital components of many of the body tissues but being insoluble in water they must be transported in the blood stream by association with complex water-soluble molecules called *lipoproteins*. Structurally, lipoproteins consist of a core of cholesterol esters and triglycerides covered by a polar surface made up of phospholipids, free cholesterol and protein components called *apolipoproteins* or apoproteins. Five principal lipoprotein classes have been identified according to their density on ultracentrifugation and by their mobility on agarose gel electrophoresis. These lipoproteins differ in size and in their relative concentrations of cholesterol and triglycerides and in the particular apoproteins associated with them. The major lipoprotein classes are chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). The apoproteins play key roles in the synthesis, processing, and tissue disposal of lipoproteins. A comparison of the five classes of lipoproteins is provided in Table 12.18. The chylomicrons are the largest of the lipoproteins and are generated from the breakdown of the long chain dietary fat in the gut. After a meal, there is transient postprandial hyperchylomicronemia, after which the chylomicrons are rapidly cleared from the blood with the help of an enzyme called *lipoprotein lipase* found in muscle and adipose tissue capillaries. After hydrolysis of the triglyceride core of the chylomicron by lipoprotein lipase, the remnant particle is called a chylomicron remnant. These *chylomicron remnants* are thought to be thermogenic and are cleared from the circulation by receptors present on the surface of the liver cells. Defects in lipoprotein lipase, or its activator (apoprotein C_2), or in the hepatocyte receptor can result in hypertriglyceridemia due to hyperchylomicronemia.

Table 12.18 Comparison of major plasma lipoproteins

Class	*Diameter (nm)*	*Density (g/ml)*	*Associated apoprotein*	*Electrophoretic mobility*	*Major lipid constituent*
HDL	5–13	1.063–1.210	AI,AII	α	Cholesteryl esters
LDL	20–28	1.019–1.063	B100	β	Cholesteryl esters
IDL	25	1.006–1.019	B100,CIII,E	Slow pre-β	Cholesteryl esters and triglycerides
VLDL	25–75	0.95–1.006	B48,CI-III,E	Pre-β	Endogenous triglycerides
Chylomicrons	100–1000	<0.95	AI,AII,B48, CI–III,E	At origin	Dietary triglycerides

HDL=high density lipoprotein, LDL= low density lipoprotein, IDL= intermediate density lipoprotein, VLDL= very low density lipoprotein

The VLDL represents the intermediate size lipoprotein that is produced endogenously by the liver and the intestine. The VLDL particles in systemic circulation are hydrolysed by lipoprotein lipase, and the remaining VLDL remnant is called IDL or intermediate density lipoprotein. After their formation, intermediate density lipoproteins are removed from circulation by the liver by means of binding to the LDL receptors. Elevated levels of LDL are thought to predispose to premature ischemic heart disease and peripheral artery disease. LDL is the major carrier of cholesterol to various tissues including nerve tissues, cell membranes and other cells that require cholesterol for metabolic functions. LDL is synthesised from the VLDL remnants (IDL) or by direct hepatic production of LDL. LDL particles are recognised by specific LDL receptors on the surface of certain non-hepatic and hepatic cells. Elevated levels of LDL result in hypercholesterolemia and increased atherosclerosis. The high density lipoproteins are produced by the liver and the gastrointestinal tract, and by the peripheral catabolism of chylomicrons and VLDLs. About eighty per cent of LDL in the plasma is removed each day by the LDL receptor pathway. The remaining twenty per cent is degraded by a scavenger cell system in the phagocytes of the reticuloendothelial system. As the membranes of the parenchymal cells and the scavenger cells undergo turnover, cholesterol is released into the plasma where it binds initially to HDL. The cholesterol esters that appear on the surface of the HDL are then transferred to VLDL and finally to the LDL. Thus, HDL serves as an important functionary in the *reverse cholesterol transport* whereby cholesterol released from extrahepatic tissues is transported back to the liver. HDL also plays an important role in triglyceride metabolism. HDL serves as a reservoir for certain apoproteins (Apo C_2), which are needed to activate the enzyme lipoprotein lipase. Thus when HDL levels are low, triglyceride levels are high due to impaired catabolism. Another lipoprotein which has been established as an independent risk factor for coronary artery disease is *lipoprotein A*. This lipoprotein is structurally similar to both LDL and to plasminogen. However, lipoprotein A appears to be regulated independent of LDL and other lipoproteins and carries an independent relation to overall coronary risk. It has been postulated that because of the structural similarity to plasminogen, high levels of lipoprotein A may inhibit the naturally occurring thrombolytic activity of tissue plasminogen, thus predisposing to a thrombotic state.

Hyperlipoproteinemia and familial syndromes

An elevation of fasting plasma levels of triglycerides or cholesterol is called hyperlipidemia. An isolated elevation in plasma triglyceride levels indicates that either the concentration of chylomicrons or of VLDL is increased. Similarly, an isolated elevation of plasma cholesterol nearly always indicates that the concentration of LDL is increased. Frequently, however, both triglycerides and cholesterol levels are elevated. A comparison of important genetic hyperlipoproteinemia syndromes is provided in Table 12.19. It must be borne in mind, however, that non-genetic forms of hyperlipidemia are more frequent as compared to the genetic forms in subjects with coronary heart disease.

Familial combined hyperlipidemia, an autosomal dominant trait, is the commonest monogenic lipid disorder among survivors of acute myocardial infarction. It is first expressed in adulthood with elevation of both cholesterol and triglyceride levels. This disorder is associated with an increase in risk for premature atherosclerosis. *Familial hypercholesterolemia* is also an autosomal dominant disorder with a high degree of penetrance. The primary genetic defect in familial hypercholesterolemia is a mutation in the LDL receptor gene. The LDL receptor is located in coated pits on the surface of hepatocytes and other extrahepatic cells.

Table 12.19 Comparison of hyperlipidemia

Type	*Clinical name*	*Elevated lipoproteins*	*Elevated lipids*	*Inheritance*	*Risk for CAD*	*Risk for pancreatitis*	*Clinical features*	*Treatment*
I	• Familial chylomicronemia • Familial (exogenous) hypertriglyceridemia	chylomicrons	triglycerides	AR	→	↑↑↑	pancreatitis, eruptive xanthomas, lipemia retinalis	low fat intake, no alcohol
IIa	• Familial hypercholesterolemia	LDL	cholesterol	AD	↑↑↑	–	xanthelasma, juvenile arcus, tendinous* xanthomas, coronary disease	low fat diet, niacin / bile acid sequestrant, HMG-CoA reductase inhibitors
IIb	• Familial combined hyperlipidemia	LDL+ VLDL	cholesterol + triglycerides	AD	↑↑	–	Obesity, hyperuricemia, hyperglycemia, coronary artery disease	above (IIa) + fibric acid derivatives
III	• Broad beta disease • Familial dysbetalipoproteinemia • Remnant disease	IDL	triglycerides + cholesterol	unclear	↑↑↑	?	coronary and peripheral vascular disease, planar and tuberous ** xanthomas	weight reduction, low fat diet, niacin or fibric acid derivatives
IV	Endogenous hypertriglyceridemia	VLDL	triglycerides ± cholesterol	sporadic, AD	↑	↑↑	obesity, hyperuricemia, hyperglycemia,	weight reduction, low fat diet, no alcohol, niacin or fibric acid derivatives
V	Mixed hypertriglyceridemia	VLDL + chylomicrons	triglycerides ± cholesterol	hetero-geneous	→	↑↑↑	Pancreatitis, eruptive xanthomas, lipemia retinalis	as above (IV)

↑, ↑↑ and ↑↑↑ = mild, moderate and marked increase, respectively; → = no effect, LDL = low density lipoproteins, VLDL = very low density lipoprotein, IDL = intermediate density lipoproteins (remnants). * Xanthomas are deposits of cholesterol. Tendinous xanthomas occur on tendons; ** Tuberous xanthomas occur over elbows or knees; CAD = coronary artery disease

A defective receptor may be associated with either absent or defective binding to the LDL particle or faulty internalisation of the LDL receptor complex. The gene frequency for this disorder is as high as one per 500 people in the West. Heterozygous individuals with a single dose of the mutant allele have cholesterol levels in the range 350–450 mg/dl, and are non-responsive to a cholesterol-lowering diet. These individuals develop deposits of cholesterol called *xanthomas* along their tendons, particularly the Achilles tendon and the tendons overlying the metacarpals. Cholesterol deposits in the cornea are recognised as the corneal arcus. Homozygous individuals have a double dose of the mutant allele and have serum cholesterol in the range 600–1000 mg/dl. Symptoms develop in the first decade of life with development of xanthomas over the tendons and in the interdigital webs. Cholesterol deposits on the aortic valve leaflets can cause xanthomatous aortic stenosis. These individuals may die as a result of severe coronary atherosclerosis in the first decade of life.

Familial lipoproteinemia, also called *remnant disease,* is characterised by elevation of intermediate density lipoproteins in the plasma of affected individuals. The clinical disorder is characterised by the appearance of xanthomas in the palms of the hands and over tuberosities (known as *tuberoeruptive xanthomas*), that is, tibial tuberosities and the elbows. Tendinous xanthomas which are common in familial hypercholesterolemia are rare in this disorder. There is equal elevation of both cholesterol and triglyceride levels in the plasma. Premature coronary artery disease and peripheral vascular disease are common in this disorder. *Familial hypertriglyceridemia* is an autosomal dominant disorder characterised by elevated triglyceride levels in the blood, usually in the range of 200–500 mg/dl. The risk for coronary artery disease in these patients is less clearly delineated.

Secondary hyperlipidemia

The common causes of secondary hyperlipidemia include systemic disorders like diabetes mellitus, chronic alcohol abuse, chronic renal failure, hypothyroidism, nephrotic syndrome and severe liver dysfunction. Several drugs which are commonly used can cause hyperlipidemia. These include the thiazide group of diuretics, oral contraceptives and corticosteriods. A search for an underlying secondary cause for hyperlipidemia is essential when investigating any individual with raised serum cholesterol or triglyceride levels.

Hyperlipidemia and coronary risk

Hypercholesterolemia is associated with increased incidence of premature coronary artery disease. There is a continuous gradient of increasing risk of coronary artery disease as the cholesterol level rises from a value of 180 mg/dl. As a working rule, hyperlipidemia is considered to be present when plasma cholesterol level exceeds 200 mg/dl (5.2 millimoles per litre) or the triglyceride level exceeds 200 mg/dl (2.2 millimoles per litre). Several degrees of hyperlipidemia (cholesterol greater than 300 mg/dl or triglyceride greater than 500 mg/dl) usually reflects an underlying genetic disorder, especially when xanthomas are present. It has been recommended that a blood cholesterol level less than 200 mg/dl (5.2 millimoles per litre) be considered as *desirable.* A level of cholesterol varying between 200–239 mg/dl (5.2 to 6.1 millimoles per litre) is considered as *borderline high* and a cholesterol level greater than 240 mg/dl (greater than 6.2 millimoles per litre) is considered as *high.* When an individual has a blood cholesterol value greater than 240 mg/dl or has borderline cholesterol values with either definite coronary artery disease or two or more risk factors for coronary artery disease, it is recommended that lipoprotein analysis be used to guide risk assessment and therapy. Total cholesterol, triglycerides and HDL cholesterol can be measured on a single fasting blood sample. The LDL cholesterol

can then be calculated according to the formula

LDL cholesterol = total cholesterol – (HDL cholesterol – triglyceride divided by 5).

A level of LDL cholesterol less than 130 mg/dl (3.4 millimoles per litre) is considered desirable. LDL cholesterol levels in the range of 130 to 159 mg/dl (3.4–4.1 millimoles per litre) are considered borderline high. LDL cholesterol levels more than 160 mg/dl (4.2 millimoles per litre) are considered high. A level of LDL cholesterol more than 160 mg/dl or a level in the range 130–159 mg/dl in the presence of definite coronary artery disease with two or more risk factors usually merits treatment. Guidelines for screening and treating subjects with high blood cholesterol are shown in Fig 12.34.

Management General measures which are advisable in subjects with hyperlipidemia include regular exercise, reduction of body weight and a cessation of cigarette smoking. Secondary causes of hyperlipidemia must be investigated and treated. The initial step of treatment is institution of a cholesterol lowering diet. An initial diet with a total cholesterol content less than 300 mg/day, restriction of total fat to 30 per cent of the calories and saturated fat to less than 10 per cent of the calories, is instituted for a total duration of three months. If the desirable levels of cholesterol or LDL cholesterol are not achieved at the end of this period, a revised diet can be instituted restricting the saturated fats to seven per cent of total calories and limiting the dietary cholesterol to 200 mg/day. If rigorous dietary measures are not effective over a period of six months, drug therapy should be considered. Other supplementary dietary measures which can be tried are an increased consumption of dietary fibre (such as oat bran that lowers serum cholesterol), or supplementation with fish intake that reduces triglyceride levels. There are six main classes of hypolipidemic drugs (shown in Table 12.20). The bile acid sequestrants lower LDL levels but can elevate triglyceride levels. The fibric acid derivatives lower LDL cholesterol but are particularly effective in lowering triglyceride levels, and in raising HDL cholesterol levels. Nicotinic acid derivatives lower both LDL cholesterol and VLDL cholesterol. The HMG coenzyme A reductase inhibitors are potent at lowering raised LDL cholesterol levels but also lower triglyceride levels and increase HDL cholesterol levels. The drug probucol lowers LDL cholesterol but does not affect triglyceride levels. It may lower levels of HDL cholesterol to a variable degree. Subjects with elevated triglyceride levels are best treated with fibric acid derivatives or with nicotinic acid. Subjects with isolated elevation of cholesterol levels can be treated with HMG coenzyme A reductase inhibitors, bile acid sequestrants, nicotinic acid or probucol. When both the triglyceride and the cholesterol level are elevated, a combination of a fibric acid derivative and a bile acid sequestrant or nicotinic acid is ideal. Sometimes when monotherapy with a single hypolipidemic drug is ineffective, a combination of drugs can lower the lipid levels effectively. Such combination therapy may be required and is especially beneficial in subjects with familial hypercholesterolemia.

Myocardial Ischemia

Pathophysiology Myocardial ischemia refers to the lack of oxygen for the myocardial cells consequent to inadequate perfusion. It is a complex interplay of myocardial oxygen demand and myocardial oxygen supply. Myocardial ischemia can occur when myocardial oxygen demand exceeds myocardial oxygen supply. This may be due to an increase in the myocardial oxygen demand over and above the basal requirements, or due to a decrease in myocardial oxygen supply as compared to the basal state, or a it may arise from a combination of both the factors. Myocardial oxygen consumption is determined principally by three factors:

Assess cardiovascular risk factors

Risk factors	*Definition*
Positive	
Age	Male ≥ 45 yr: Female ≥ 55 yr. or premature menopause without estrogen replacement therapy
Family history of premature coronary artery disease	Definite myocardial infarction before age 55 in first-degree male relative, or before age 65 in first-degree female relative
Current cigarette smoking	
Hypertension	Blood pressure ≥140/90 mmHg confirmed by measurement on several occasions, or taking antihypertensive medication
Low HDL cholesterol level	< 35 mg/dl; confirmed by measurement on several occasions
Diabetes mellitus	
Negative	
High HDL cholesterol level	≥ 60 mg/dl subtract one risk factor if HDL cholesterol level is high

Assess for macrovascular disease

Macrovascular disease absent → TC and HDL (non-fasting acceptable)

Macrovascular disease present → Fasting lipoprotein analysis

After fasting lipoprotein analysis:

TC<200
HDL >35: remeasure TC and HDL within 5 years or with physical exam; supply general educational materials
HDL <35;
lipoprotein analysis (see next column)

TC 200–239
HDL > 35 + <2 other risk factors: remeasure TC and HDL in 1–2 years; instruct in diet, physical activity, risk factor reduction
HDL < 35 or >2 other risk factors: lipoprotein analysis (see next column)

TC <240
lipoprotein analysis (see next coloumn)

LDL <130
remeasure TC and HDL within 5 years; supply general educational materials

LDL 130–159
< 2 other risk factors:
supply information on Step I diet and physical activity. Reevaluate annually, including lipoprotein analysis, risk factor reduction;
≥ 2 other risk factors:
clinical evaluation; initiate dietary therapy

LDL > 160
Clinical evaluation; initiate dietary therapy

LDL ≤ 100:
individualised instruction on Step II diet and physical activity

LDL > 100:
clinical evaluation; initiate cholesterol-lowering therapy

Dietary therapy for elevated plasma cholesterol level

*Nutrient**	*Recommended Intake*	
	Step I diet (primary prevention)	Step II diet (primary or secondary prevention)
Total fat	≤ 30% of total calories	
Saturated fatty acids	≤10% of total calories	
Polyunsaturated fatty acids	8% to 10% of total calories	< 7% of total calones
Monounsaturated fatty acids	≤ 15% of total calories	
Carbohydrates	≤ 55% of total calories	
Protein	Approx 15% of total calories	
Cholesterol	< 300 mg/day	< 200 mg day
Total Calories	To achieve and maintain desirable weight	

Fig 12.34 U.S. National Cholesterol Education Program Adult Treatment Panel guidelines

Table 12.20 Drugs for the treatment of hyperlipidemia

Drug	Prototype	Mechanism of action	Primarily lowers		Effect on lipoproteins			Indications (hyperlipidemia)	Side effects
			Cholesterol	Triglyceride	VLDL	LDL	HDL		
1. Bile acid sequestrants	• Cholestyramine 12–32 g/day • Colestipol 5–30 g/day	increase excretion of bile acids in stool	+	–	0/↑	↓	0/↑	IIa, IIb	constipation, nausea, bloating, abdominal pain, drug interactions
2. Fibric acid derivatives	• Gemfibrozil 600 mg bd • Clofibrate 1 g bd	activate lipoprotein lipase	–	+	↓	0	0/↑	IIb, III, IV, V	cholelithiasis, hepatitis, myositis, abdominal pain, nausea
3. Nicotinic acid derivatives	• Nicotinic acid 1–3 g tid	inhibit hepatic synthesis of triglycerides, inhibit lipolysis in adipocytes	+	+	↓	↓	↑	Iia, IIb III, IV, V	flushing, hyperglycemia, gout, hepatitis
4. HMG coenzyme A inhibitors	• Lovastatin 20–80 mg/day • Simvastatin 5–40 mg/day • Pravastatin 10–40 mg/day	inhibit cholesterol biosynthesis, increase LDL clearance	+ +	– –	0/↓	↓	0/↑	IIa, IIb	hepatitis, myositis, rhabdomyolysis, lenticular opacities
5. Inhibitors of LDL oxidation	• Probucol 500 mg bd	inhibit lipid peroxidation	+	–	0/↓	↓	↓	IIa, IIb	abdominal pain, prolonged Q-T, diarrhea, bloating, low HDL

↑ = Increase, ↓ = decrease, 0=no effect, VLDL = very low density lipoprotein, LDL = low density lipoprotein, HDL = high density lipoprotein, HMG = 3-hydroxy, 3-methyl glutaryl.

1. *systolic wall tension* which is in turn directly related to systolic arterial pressure and the intraventricular radius, and inversely related to the myocardial wall thickness;
2. *heart rate* (a faster rate increases oxygen demand); and
3. *myocardial contractility* (increased contractility leads to increased oxygen demand).

An indirect estimate of myocardial oxygen demand is provided by the *double product* which is obtained by multiplying the heart rate by the systolic blood pressure. However, this index does not consider myocardial contractility. The supply of oxygen to the myocardium depends on the amount of blood flowing through the coronary arteries and the ability of the myocardial cells to extract oxygen from the blood. Unlike the other organs of the body, the heart has the unique property of near-maximal oxygen extraction by the cells at a resting state. Therefore, myocardial oxygen supply is principally affected by the amount of blood flowing through the coronary arteries, that is, *coronary perfusion*. The two principal determinants of coronary perfusion are the perfusion pressure and the resistance of the coronary vascular bed. Coronary perfusion pressure is directly dependent on the aortic diastolic pressure because most coronary flow occurs during diastole. The duration of diastole is also therefore an important determinant of myocardial blood flow; tachycardia shortens diastole and can reduce blood supply to the myocardium. Coronary artery resistance is influenced by numerous factors which are as yet incompletely understood. It has been recently appreciated that a factor called *endothelial derived relaxing factor* (EDRF), believed to be nitric oxide, is released from the vascular endothelium into the smooth muscle cells in the wall of the vessel, to allow vascular relaxation. A counterregulatory agent called endothelial derived constricting factor *(endothelin)* has also recently been discovered. Coronary vascular resistance is affected by this complex interplay of local hormonal and metabolic factors along with neural influences. Narrowing of the epicardial coronary arteries by atherosclerotic plaques can cause dysfunction of the vascular endothelium with a decrease in the release of EDRF. Generally pulsatile flow is maintained until the luminal stenosis reduces the cross-sectional area by approximately 75 per cent. A fixed reduction of the luminal cross-sectional area by 70–75 per cent is therefore considered as significant coronary artery stenosis. It must, however, be remembered that a lesser degree of cross-sectional area narrowing may become significant when dynamic changes like vascular spasm are superimposed on the fixed obstruction and the cross-sectional area is reduced by about 70–75 per cent.

Myocardial ischemia is associated with a sequence of changes that have been called the *ischemic cascade*. This ischemic cascade refers to disturbances of the biochemical, hemodynamic, mechanical and electrical functions of the myocardium that is rendered ischemic. The first step in this ischemic cascade is the change in the myocardial cellular function with conversion from an aerobic to an anerobic metabolism. Fatty acids cannot be oxidised and glucose is broken down to lactate. The intracellular pH is reduced as also are the myocardial stores of high energy phosphate, ATP and creatine phosphate. There are associated changes due to impaired ion fluxes characterised by the leakage of potassium from the myocytes with an uptake of sodium. The next step in the ischemic cascade is a fall in the rate of ventricular myocardial relaxation indicative of ventricular diastolic impairment. This is manifested by the hemodynamic observation of an elevation of left ventricular end-diastolic pressure with the onset of ischemia. The third step in the ischemic cascade is the development of impaired systolic function which is usually regional and limited to the area of the myocardium which is rendered ischemic. When ischemia is global, global contractile failure can ensue. The fourth step in the ischemic cascade is the development of

surface electrocardiographic abnormalities. Ischemia characteristically causes repolarisation abnormalities evidenced initially by inversion of the T wave and later by displacement of the ST segment. Transient ST segment depression often indicates subendocardial ischemia, whereas transient ST segment elevation indicates more severe transmural ischemia. There are other concomitants of the ischemic cascade that may or may not occur. One important consequence is electrical instability which may lead to ventricular arrhythmias, such as, ventricular tachycardia or ventricular fibrillation. Symptoms occur in the fifth step of the ischemic cascade. These may be in the form of chest pain, angina or anginal equivalents, that is, dyspnea or a feeling of ill-being. Whenever ischemia is severe and prolonged, injury to the myocardium results. This injury is termed *infarction*. Myocardial injury is associated with cessation of contraction and depletion of high energy stores. There is a wavefront of cell death that proceeds from the subendocardium towards the subepicardium culminating in a transmural infarct. The duration of ischemia necessary for completion of cell death averages from 2–6 hours in human beings. Infarction on occasion however may progress in a stuttering fashion, being determined by the amount of collateral flow into the ischemic region and by the presence or absence of reperfusion. In the absence of reperfusion, cellular death occurs. When reperfusion occurs early in the course of infarction, either by means of therapeutic measures or spontaneously, a series of events occur which are referred to as *reperfusion injury*. The restoration of oxygenated blood flow into the area of injury results in increase in the tissue water, calcium, and sodium, and the disruption of the irreversibly injured myocytes that are unable to regulate their cellular volume. Though the subendocardial cells may die, some viable cells in the subepicardial and the midmyocardial layers of the ventricular wall are salvaged.

It was earlier believed that following severe ischemia of the myocardium, the myocardium was either irreversibly injured or it recoverd promptly. However, it has become increasingly clear that *myocardial dysfunction* may be prolonged after a brief episode of severe ischemia. Two other conditions described are *myocardial stunning* and *myocardial hibernation*. Once there is severe persistent chronic ischemia, myocardial function can be chronically depressed. This phenomenon is called myocardial hibernation. When blood flow is restored to such myocardium (myocardial revascularisation) myocardial functional recovery can be very prompt. Similarly, after a brief episode of severe ischemia, when perfusion is restored, contractility may not return immediately and the myocardium may continue to be dysfunctional. Such a phenomenon of myocardial dysfunction occurring despite reperfusion is called *myocardium stunning*. It has become important to recognise these phenomena of myocardial hibernation and myocardial stunning because the myocardium may have impaired function and yet may be *viable*. Viability is identified by the persistence of intermediary metabolism that can be recognised by sophisticated tests such as positron emission tomography using fluorine 18-deoxyglucose to measure glucose uptake by these viable but dysfunctional myocytes. Fig 12.35 demonstrates the pathophysiology of the ischemic syndromes.

Chronic Stable Angina Pectoris

Angina pectoris is the brief discomfort in the chest or adjacent areas arising due to myocardial ischemia. It may be associated with myocardial dysfunction, without myocardial necrosis.

Pathophysiology Angina pectoris arises due to a transient increase in myocardial oxygen demand as compared to the myocardial oxygen supply. It has been postulated that ischemia causes intracellular acidosis and elevated

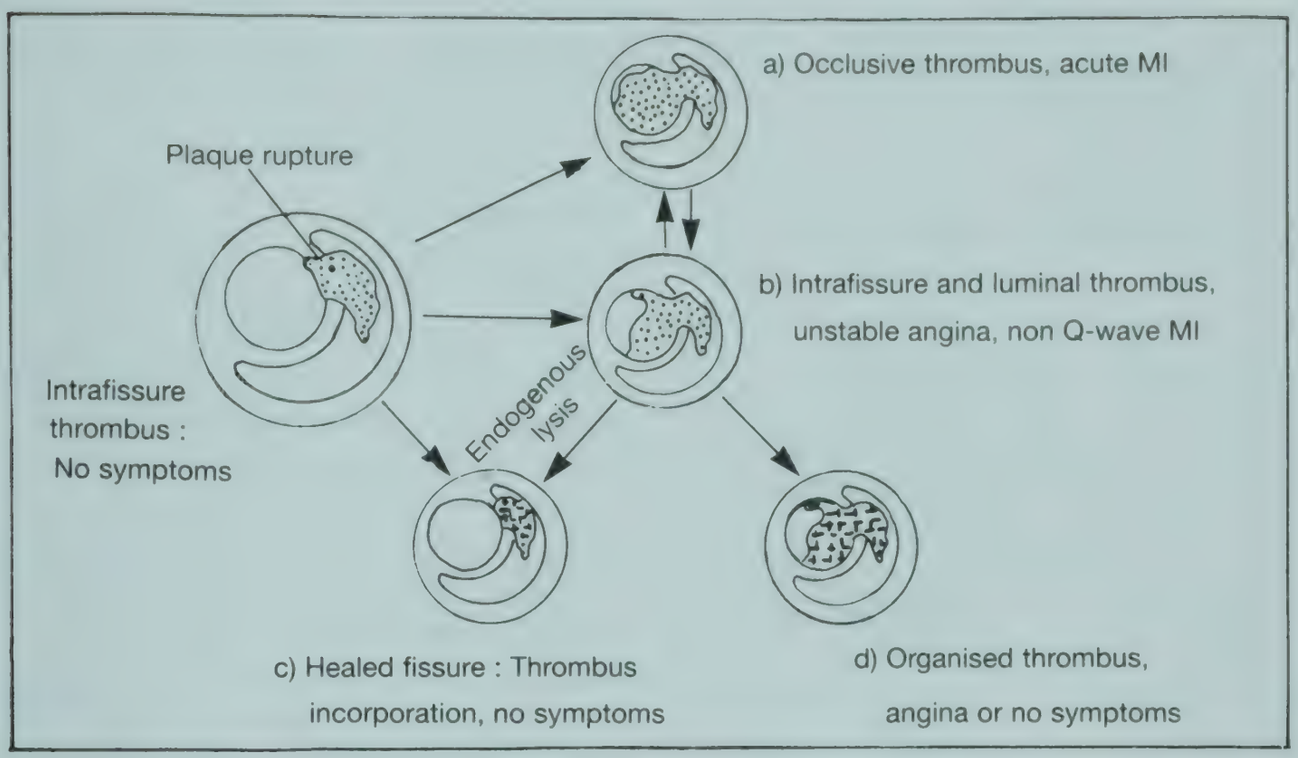


Fig 12.35 Pathophysiology of ischemic syndromes: plaque rupture leads to the formation of a fissure with flowing blood contacting intraarterial structures and forming an intrafissure thrombus. This may not lead to symptoms except for possible sudden onset of coronary spasm or vasoconstriction associated with arterial injury. The thrombus may progress to a luminal thrombus and cause unstable angina or non-Q wave myocardial infarction (MI) (b), or total occlusion, which is often associated with transmural or Q wave MI (a). Intraluminal thrombus may undergo endogenous lysis with healing of the fissure and no progression of disease or symptoms (b to c). Intraluminal thrombus may organise, leading to progression of disease with or without subsequent symptoms (d).

potassium concentrations within the cell that triggers the release of agents such as adenosine, bradykinin, histamine or serotonin; these agents stimulate the sensory endplates of intracardiac sympathetic nerves supplying the region which is rendered ischemic. These sensory endplates are a network of unmyelinated nerve fibres that are found between the cardiac muscle fibres and which travel to a cardiac plexus and then ascend to the sympathetic ganglia in the region C7 to T4. These impulses are then transmitted to a pool of secondary neurons that is common to both somatic and visceral afferent impulses. Since the stimuli from the visceral organs is excessive, the second order neurons that are also receptors for somatic impulses, are excited and the discomfort will be perceived as arising from the peripheral dermatomes that have the same afferent nerve supply as the heart. This is termed *referred pain*. Since these second order neurons have connections to the brachial plexus and the cervical roots, angina may be perceived as pain radiating around the medial aspect of the arm or into the neck or the jaw.

Clinical features The pain of angina pectoris is characterised by three important features:

1. the location and the character of the pain,
2. the duration of the pain, and
3. the presence of precipitating factors and relieving factors.

Classic angina pectoris is experienced as a substernal chest discomfort that may be a

sensation of pressure, heaviness, a squeeze, or occasionally even a sensation of burning. When the patient describes the sensation by clenching the fist over the sternum (known as *Levine's sign,* the chest pain is highly likely to be angina. However, occasionally the sensation may be more vague and like a visceral discomfort rather than exhibit any of the specific characteristics listed above. Though the site of discomfort is usually substernal, the pain commonly radiates down the ulnar surface of the left arm, or occasionally the right arm. The pain of angina may radiate to the neck or to the jaw or to the throat or even to the upper part of the abdomen. The pain seldom radiates below the umbilicus or above the jaw. The discomfort of angina pectoris usually lasts for some time between one and fifteen minutes. The pain of angina is typically brought on by exertion or some form of stress and is relieved by rest, or with the use of sublingual nitroglycerin (within ten minutes). When any chest pain does not meet all the three features of angina pectoris described above, it is not classic angina pectoris. When two out of these three features is present, the chest pain can be considered as atypical chest pain that could still be angina. When only one of the three features is present, the chest pain is most probably due to a non-cardiac cause. Thus, chest pain that is brief, (lasting less than five seconds), or prolonged (lasting for more than 20–30 minutes), which is localised to a very small area like the size of the top of a finger, or which is aggravated by deep breathing, is unlikely to represent angina pectoris. In patients with angina pectoris there is a wide variation in the threshold of activity that brings about the chest pain. Some patients can predict with precision the amount of physical activity that can cause angina (*fixed threshold angina*) while there are other patients in whom the magnitude of physical activity required to bring out angina can vary from day to day (*variable threshold angina*). Physical findings during an episode of angina may include auscultatory evidence of a fourth heart sound or a transient systolic murmur representing ischemic papillary muscle dysfunction. Usually the blood pressure and heart rate product (double product) is elevated during an episode of angina. The presence of characteristic ST segment changes on an ECG during an episode of chest pain identifies the chest pain as an attack of angina pectoris.

Investigations In patients with atypical chest pain, an exercise stress test can be used as a diagnostic tool (section 12.3). An exercise test positive for myocardial ischemia is good evidence that the chest pain is angina pectoris. Subjects with classic angina pectoris do not require an exercise stress test as a diagnostic tool. However, an exercise stress test in these patients can be of prognostic value. Regarding the use of the exercise stress test as a diagnostic tool, it would be proper to recapitulate that the predictive value of the stress test varies with the population being studied (*Bayes' theorem*). Thus, in a population with a statistically low prevalence of coronary artery disease, such as a young women with atypical chest pain, the positive predictive value of a stress test is low although the negative predictive value is high. Similarly, in subjects with a high likelihood of coronary artery disease, such as men over the age of sixty with multiple coronary risk factors, the positive predictive value is high but the negative predictive value of a stress test is low. The exercise stress test is also used as a prognostic tool since the mere presence of angina is a poor marker of the extent and severity of underlying coronary artery disease. Thus, presence of exercise-induced hypotension (a drop in the systolic blood pressure during exercise below the basal value), presence of severe ST segment depression at a low exercise workload and the presence of a downsloping or horizontal ST segment depression in multiple leads identify patients with multivessel coronary artery disease.

Certain patients with angina pectoris have chest pain at rest and not during exercise. This

Table 12.21 Comparison of commonly used antianginals

Drug	*Dose*	*Duration of action*	*Comments*
A. Nitrates			
Sublingual nitroglycerin	0.3–0.6 mg when needed	10–30 minutes	effect in 2–5 minutes; headache, hypotension common; store in airtight dark bottle, replace every 6 months
Isosorbide dinitrate	5–40 mg tid	4–6 hours	headache, tolerance; allow 12-hour nitrate-free interval
Isosorbide mononitrate	10–20 mg bid	6-8 hours	as above
Nitroglycerin SR	2.5–9.0 mg qd	12–24 hours	headache, hypotension
Nitroglycerin ointment (2%)	0.5–2.0 inch	3–8 hours	absorption often not predictable
Transdermal Nitropatch	5–15 mg	12–16 hours	remove patch after 12 hours
B. Beta-blockers			
1. Beta-1 selective			
Atenolol	50–100 mg qd	6–8 hours	safe in asthma, bronchospastic conditions, diabetes, peripheral vascular disease
Metoprolol	50–100 mg bid	3–4 hours	as above
Acebutalol	200–600 mg bid	3–4 hours	as above; has ISA, causes less bradycardia
2. Nonselective			
Propranolol	20–80 mg qid	4–6 hours	long safety record; care if CHF present
Propranolol LA	80–160 mg qd	12 hours	long-acting preparation increases compliance
Nadolol	40–160 mg qd	20–24 hours	lipid soluble (reduced CNS side-effects)
C. Calcium channel blockers			
1. First-generation			
Verapamil	80–120 mg tid	6–8 hours	constipation, A-V block, worsening of CHF
Verapamil SR	120–240 mg bid	12–24 hours	
Diltiazem	30–90 mg qid	6–8 hours	
Diltiazem SR	60–120 mg bid	12–24 hours	
Nifedipine	10–30 mg tid	6 hours	hypotension, flushing, headache, edema, worsening of angina*
Nifedipine XL	30–120 mg qd	24 hours	
2. Second-generation			
Amlodipine	2.5–10 mg qd	24 hours	no reflex tachycardia, no effect on sinus or AV node conduction
Felodipine	5–10 mg bid	12 hours	limited experience
Isradipine	2.5–10 mg bid	12 hours	

SR = sustained release, XL = extended release, LA = long acting
qd = once daily, bid = twice daily, tid = three times daily, qid = four times daily ISA = intrinsic sympathomimetic activity
* there is a report of an adverse effect of short-acting preparations when given after myocardial infarction.

form of angina is called *variant angina* or *Prinzmetal's angina.* It is caused by focal spasm of the proximal epicardial coronary arteries. Ambulatory electrocardiography (Holter monitoring) is useful for identifying these patients; episodes of chest pain are associated with elevation of the ST segment. Thallium-201 myocardial perfusion scintigraphy is often used in combination with the exercise stress test to increase the sensitivity of the stress test, with an increase in the specificity too. However, it should be borne in mind that thallium scintigraphy is expensive and available at few centres in India. Hence it should not be ordered routinely. Thallium-201 scintigraphy adds little to the diagnostic information in a subject with a strongly positive exercise ECG who is also felt clinically to have a high pretest probability of having coronary artery disease. It may however be combined with the exercise stress test when the latter is positive in a subject with a very low pretest probability of coronary artery disease. It can also be used in the place of the exercise stress test in subjects with an abnormal resting ST segment on the ECG due to left bundle branch block, left ventricular hypertrophy or other conduction disturbances. In subjects who cannot exercise adequately, thallium scintigraphy can be performed with the use of intravenous dipyridamole or intravenous dobutamine. Exercise stress echocardiography has also been used for the diagnosis of myocardial ischemia. Similarly, exercise radionuclide ventriculography (exercise MUGA) has been used for the diagnosis of myocardial ischemia. Both these tests involve the detection of regional wall motion during the period of myocardial ischemia. Cardiac catheterisation is used in patients with strongly positive exercise stress responses or in patients with severe angina pectoris that cannot be controlled with medication. It helps in providing the anatomic basis of the disease and helps in further therapeutic decisions. The decision to perform a particular invasive or non-invasive test is taken in the context of other data of the patient derived from history, physical examination and other relevant tests.

Natural history The natural history of untreated angina pectoris depends on the underlying coronary anatomy. Thus, patients with disease of one coronary vessel have an annual mortality of less than 4 per cent, patients with two vessel disease have an annual mortality of 7–10 per cent, and sucbjects with three vessel coronary disease have an annual mortality of 10–12 per cent. Patients with obstruction of the left main coronary artery are at particularly high risk, with an annual mortality of 15–25 per cent.

Management The goal of therapy in chronic stable angina pectoris is to eradicate episodes of symptomatic myocardial ischemia, arrest the progression of disease, prevent future cardiac events and if possible, bring about the regression of established coronary disease. The ideal therapeutic regimen, therefore, is one that maximises myocardial oxygen supply and minimises myocardial oxygen demand without significant clinical adverse side effects. Every patient of angina pectoris must be considered for modification of cardiac risk factors. Weight reduction, regular exercise, cessation of cigarette smoking, control of diabetes mellitus and hypertension and reduction of serum cholesterol and triglyceride levels are essential. Concomitant diseases which compromise oxygen supply, such as anemia, must be identified and vigorously treated. The drug treatment of chronic stable angina pectoris consists of one or more of three classes of drugs either alone as monotherapy or as combination therapy. Table 12.21 provides comparison of these three classes of drugs. Nitrates remain a primary component of antianginal therapy. The primary antianginal effect of nitrates is due to an increase in venous capacitance leading to a reduction in ventricular volume and pressure and consequent improvement in subendocardial perfusion. Dilatation of epicardial stenosis,

dilatation of coronary collaterals, and afterload reduction are secondary mechanisms which augment this primary effect. It has been postulated that nitrates are converted within the vascular smooth muscle cells into the reactive nitric oxide free radical which in turn triggers smooth muscle relaxation. Whereas nitrates primarily increase myocardial oxygen supply, the beta adrenoceptor blockers reduce myocardial oxygen demands during activity when surges of increased sympathetic activity occur. These drugs also lower myocardial oxygen consumption by inhibiting myocardial contractility at rest and by diminishing the heart rate at rest. A further salutary effect is mediated by the effect of these drugs in reducing arterial pressure and thereby decreasing ventricular afterload. Beta-blockers reduce the frequency of anginal episodes and raise the anginal threshold by attenuating the chronotropic and inotropic responses to adrenergic stimulation by competitively inhibiting the effect of circulating catecholamines on beta adrenoceptors. The calcium channel blockers on the other hand interfere with the entry of calcium into the myocytes and vascular smooth muscle cell and thereby cause coronary and peripheral vasodilatation. A reduction in peripheral vascular resistance also serves to diminish myocardial oxygen demand. These agents are particularly effective in the treatment of vasospastic angina (Prinzmetal's angina). The choice of the antianginal agent depends upon the clinical profile of the patient. Thus, patients with variable threshold angina seem to respond better to a calcium channel antagonist whereas patients with a fixed anginal threshold seem to respond better to a beta-blocker. When there is clinical presence of moderate to severe left ventricular dysfunction, beta-blockers or the calcium channel blocking agent verapamil can exacerbate the degree of cardiac failure. Similarly, in patients with sick sinus syndrome or significant atrioventricular conduction disturbances, beta-blockers and verapamil are often contraindicated, with the calcium channel blocker nifedipine being the agent of choice. Beta-blockers are also avoided in subjects with a history of asthma or severe chronic obstructive airway disease and in people with a significant history of depression, sexual dysfunction, sleep disturbances or nightmares. It must be borne in mind that the combination of a beta-blocker and a calcium antagonist may not be consistently better than the use of either agent alone if administered in the maximum tolerated dose. However, a combination treatment may have to be used if the maximal dose of either drug is associated with clinically significant side effects. Though antiplatelet agents such as aspirin have no proven efficacy in the treatment of stable angina pectoris, they can be used in lower doses in these patients in view of the emerging evidence supporting a rule for platelets in the progression of chronic stable angina pectoris to the unstable coronary syndromes.

Non-medical treatment

Coronary artery bypass graft (CABG): Coronary artery bypass grafting consists of the use of a venous or arterial conduit one end of which is anastamosed to the aorta and the other end is anastamosed to the diseased coronary segment distal to the obstruction. The graft restores coronary blood flow beyond the obstruction. The saphenous vein from the leg is used for bypassing obstructions in the distal branches of the right coronary artery and the circumflex coronary artery as well as the diagonal branch of the left anterior descending artery. The left internal mammary artery is a preferred conduit for bypassing obstructions in the left anterior descending coronary artery. The arterial grafts last relatively longer and are free of the complications of accelerated atherosclerosis that commonly occur in saphenous venous grafts, thereby maintaining the patency of the bypass graft for a longer duration. Several large randomised clinical trials have provided information as to which patients with chronic stable angina pectoris benefit from surgical

therapy as compared to medical therapy. Coronary artery bypass grafting clearly prolongs survival in patients with significant left main coronary artery disease and in patients with multivessel disease with impaired left ventricular function. There is some evidence that in patients with three vessel disease and normal ventricular function, surgical therapy may be better than medical therapy in the presence of a history of severe angina pectoris or prior myocardial infarction, and in the presence of resting ST segment depression on the electrocardiogram. In patients with two vessel disease, there may be some benefit of surgical therapy over medical therapy if one of the two vessels involved by the disease is a proximal part of the left anterior descending coronary artery. Though no survival benefit has been demonstrated in other subjects with two vessel disease or single vessel disease, CABG is still beneficial in subjects with refractory angina. In these subjects, though there may be no overall improvement in survival, surgical therapy is recommended for symptomatic improvement which occurs in upto ninety per cent of patients. Thus, improvement of survival and relief of symptoms refractory to medical therapy seem to be the indications for CABG in subjects with coronary artery disease. The risks of CABG include a 1–3 per cent operative mortality and a 2–5 per cent risk of perioperative myocardial infarction. The occlusion rate of saphenous venous grafts is 10 per cent at six months, 20 per cent at the end of the first year, 25–30 per cent at five years and 40–50 per cent ten years after the surgery. Venous graft patency is increased by the use of antiplatelet drugs in the postoperative period and by the aggresive use of lipid lowering drugs in subjects who are hyperlipidemic.

Percutaneous transluminal coronary angioplasty (PTCA): Percutaneous transluminal coronary angioplasty is a technique wherein a specially designed balloon catheter is positioned across the stenotic coronary artery segment; the balloon is then inflated. The inflation of the balloon to several atmospheric pressures at the site of the stenosis produces a controlled tear of the intimal layer at the site of the atherosclerotic plaque. Once this occurs, the vessel becomes more amenable to expansion by the balloon as only the elastic media and the adventitia (the outer layers of the coronary arteries) are left to resist the circumferential stretching of the vessel. The injured intima heals with retraction and absorption of the atherosclerotic material and a new endothelial layer forms over the injured area. The injured intima attracts platelets and the latter cells release growth factors which initiate multiplication of fibroblasts at the site of the angioplasty. This results in the formation of a fibrous plaque and the vessel lumen is partially or totally restored. However, when the fibrogenesis at the site of injury is exuberant, the fibrous plaque can again project into the lumen. This is referred to as *restenosis* and represents a variation of the normal repair mechanism after plaque disruption due to coronary angioplasty.

At its inception, PTCA was considered to be indicated only in subjects with symptomatic myocardial ischemia and the coronary angiographic appearance of a suitable lesion in a single coronary artery. Such a lesion was one that was proximal (easily approachable), short and discrete (so that the balloon segment of 20 mm straddles the lesion), concentric (because dilating an eccentric lesion may affect the normal thin-walled portion more), non-calcified (higher pressures are required to fracture calcific plaques) and caused severe narrowing (more than 70 per cent luminal diameter). If these ideal patients alone are subjected to PTCA, the procedure can be performed only in 10–15 per cent of all patients with coronary artery disease undergoing angiography. However, with continuous improvement and the development of sophisticated catheter systems along with growing operator experience, the use of PTCA has diversified to include dilatation of multiple lesions in multiple vessels including distal lesions, as well as branch stenosis.

It should, however, be borne in mind that patients undergoing PTCA should be candidates for coronary artery bypass grafting since surgery may be necessary if PTCA fails or if a complication arises during the procedure. Potential complications of PTCA include coronary artery dissection, coronary occlusion with a 5 per cent incidence of myocardial infarction and a 3–5 per cent incidence of emergency CABG. Further restenosis may occur after successful dilatation of the coronary lesion in 20–30 per cent of cases, usually occurring 3–6 months after the procedure. The advantages of angioplasty over coronary artery bypass surgery include the avoidance of open heart surgery, shortened duration of hospitalisation, lower initial cost and lower short term risk. Conversely, bypass surgery, with its lower recurrence rates, offers a more durable solution to the atherosclerotic process.

Randomised clinical trials are currently in progress to determine which of these procedures should be the initial treatment of choice in patients with disease of two or more coronary arteries. Several newer angioplasty techniques utilise newer intravascular devices aimed at reducing the incidence of restenosis. These devices include the atherectomy device which cuts and extracts the intracoronary plaque leaving a relatively smooth vascular surface. The intracoronary stents are similar metallic devices that are inserted into the segment of the coronary artery that is dilated; they not only prevent acute abrupt closure of the dilated vessel but can also maintain patency of the dilated segment. Lasers have also been used both as adjuncts to balloon angioplasty and as primary recanalisation devices; they can vaporise the atherosclerotic plaque leaving behind a white smooth thrombus-free lumen. The exact indication of these newer devices is being refined and developed.

Unstable Angina

Unstable angina is a clinical syndrome describing a heterogeneous group of patients who fall into one of the following four clinical categories:

1. a pattern of crescendo angina superimposed on relatively stable angina pectoris. In these patients there is an increase in the frequency, severity and duration of the angina along with a reduction in the threshold of the physical activity which provokes angina.
2. angina pectoris occurring at rest as well as with minimal exertion,
3. angina pectoris of recent onset (within one month) which is brought on by minimal exertion,
4. post-myocardial infarction angina (within two weeks of documented myocardial infarction). Usually, there are no obvious precipitating factors (primary unstable angina). When there are preexisting conditions which precipitate the unstable angina, such as anemia, tachyarrhythmias, thyrotoxicosis or fever then the condition is often called secondary unstable angina.

Pathogenesis and pathology The underlying substrate for unstable angina is atherosclerotic coronary artery disease. More than 50 per cent of patients with a clinical diagnosis of unstable angina have an underlying coronary anatomy with three vessel coronary artery disease or left main coronary artery disease. Twenty-five per cent of subjects have one vessel disease and a small number of patients have normal coronary arteries or mildly obstructive coronary artery disease. Pathologically, the atherosclerotic lesions in unstable angina are different from those of chronic stable angina. While the plaques in chronic stable angina tend to be concentric, symmetrical, with smooth borders and a broad neck, the atherosclerotic plaques in subjects with unstable angina tend to be eccentric and with overhanging edges. This finding of an eccentric stenosis with a narrow neck and scalloped borders represents an atherosclerotic plaque which is complicated by ulceration or plaque fissuring. With the use of coronary angioscopy devices which allow visualisation of the intraluminal structure of the coronary arteries,

these fissure plaques are often seen to have overlying white thrombi suggesting platelet accumulation. Thus, the underlying pathogenetic mechanism for unstable angina seems to be intermittent coronary artery occlusion due to a spasm, platelet thrombi, and thrombus formation over complicated disrupted atherosclerotic plaques.

Investigations The twelve-lead surface electrocardiogram often demonstrates transient ST segment and T wave changes in patients with unstable angina. The presence of deep T wave inversions in the anterior precordial leads is particularly ominous, often signifying proximal left anterior descending coronary artery disease. Ambulatory electrocardiographic monitoring (Holter monitoring) is of prognostic importance in subjects with unstable angina. The presence of active ischemia on Holter monitoring helps in identifying and stratifying patient groups who need early angiography and revascularisation as compared to subjects who do not have these ischemic changes and who can be managed on a conservative medical therapy regimen.

Natural history In general, the prognosis of patients with unstable angina is not as good as that of patients with chronic stable angina. Though the acute in-hospital mortality is only about 1.5 per cent, the one year mortality averages at about 10 per cent. The incidence of non-fatal myocardial infarction within the first few weeks is as high as 15 per cent and recurrent hospital admissions are required in upto 25 per cent of patients with unstable angina.

Management Recognising the fact that unstable angina pectoris is a serious and potentially dangerous condition, the patient should be admitted to the hospital and placed at bedrest in a coronory care unit. The electrocardiogram should be monitored continuously and diagnostic blood tests including serial cardiac enzyme should be carried out to rule out the myocardial infarction. Specific drug therapy is then instituted.

1. Nitrates: Nitrates are one of the key components of therapy of unstable angina, and may be administered sublingually, orally or intravenously. Intravenous nitroglycerin offers the advantage of consistent control of ischemic episodes during the first twenty-four hours after which there is the possibility of development of pharmacological tolerance. A nitrate-free interval might then be interposed or oral nitrates added at spaced intervals. The dosage of intravenous nitroglycerin is titrated to reduce the mean arterial pressure by about 10 per cent. Nitrates relieve and prevent recurrence of pain and improve global and regional left ventricular function.
2. Beta adrenoceptor blockers: In patients with unstable angina pectoris who are not already taking a beta-blocker, therapy is indicated. The dosage of beta-blockers is so adjusted that the resting heart rate is reduced to 50–60 beats per minute.
3. Calcium channel antagonists: The addition of calcium channel antagonists to beta-blockers and nitrates has proved to be useful in relieving angina and in reducing the risk of development of myocardial infarction and the need for urgent coronary artery bypass surgery. Nifedipine would seem to have an advantage when calcium channel blockers are combined with beta-blocking agents.
4. Anticoagulants and antiplatelet drugs: There is sufficient evidence to indicate the prominent role played by platelet activation and thrombus formation in the pathogenesis of unstable angina. Therefore, once a diagnosis of unstable angina is made, administration of intravenous heparin either as a continuous infusion or as intermittent intravenous boluses is extremely important. The dosage of heparin used as a continuous infusion is 1000 units per hour. Aspirin should also be administered either in combination with heparin or after the cessation of heparin therapy. The combination of aspirin

and heparin seems to be associated with a marginally increased risk of hemorrhagic complications which can be reduced with proper monitoring of partial thromboplastin time and bleeding time. About 70–85 per cent of patients with unstable angina seem to respond to this intensive medical regimen of nitrates, beta-blockers/calcium channel blockers and intravenous heparin/ aspirin.

5. Intraaortic balloon counterpulsation: In subjects with unstable angina refractory to maximum medical therapy, intra-aortic balloon counterpulsation can be instituted to stabilise the patient's condition both symptomatically and hemodynamically before the institution of a definitive revascularisation procedure either in the form of bypass surgery or coronary angioplasty. Intraaortic balloon counterpulsation consists of inserting a balloon that is positioned in the descending thoracic aorta beyond the subclavian artery and above the renal arteries; the balloon is inserted percutaneously through the femoral artery under fluoroscopic guidance. The balloon is adjusted to inflate at the aortic valve closure (the dicrotic notch of the aortic pressure tracing) and to deflate prior to the aortic valve opening. When the balloon is inflated in diastole, diastolic pressure and therefore coronary perfusion pressure is elevated, and when the balloon deflates in systole, ventricular afterload is reduced. The net effect is one of a rising stroke volume with increased myocardial perfusion that together serve to reduce myocardial ischemia.

6. Revascularisation: In patients who are refractory to maximal medical therapy, surgery appears to be the treatment of choice especially in subjects with extensive coronary artery disease and abnormal left ventricular function. An acceptable alternative is emergency percutaneous transluminal coronary angioplasty of the culprit vessel, the latter being recognised by the presence of intraluminal filling defects corresponding to intracoronary thrombi during urgent coronary arteriography.

Acute Myocardial Infarction

The term acute myocardial infarction refers to myocardial necrosis occurring as a result of diminished perfusion of the myocardium. Unlike ischemia which refers to a reversible diminution in blood supply to the myocardium, myocardial infarction constitutes irreversible injury to the myocardium.

Pathophysiology and pathology Atherosclerotic coronary artery disease underlies most cases of acute myocardial infarction. The characteristic angiographic feature of acute myocardial infarction is the presence of a totally occluding thrombus in the culprit coronary vessel. The initiating feature of acute myocardial infarction is quite similar to that in unstable angina. Thus, fissuring, ulceration, rupture or hemorrhage into an atherosclerotic plaque appears to be the initiating event with subsequent exposure of the underlying collagen and atheromatous elements to circulating platelets and clotting factors. Platelet aggregation at the surface of the complicated plaque promotes thrombosis and leads to vasoconstriction through the release of thromboxanes. These agents seem to overwhelm the endogenous vasodilators such as prostacyclin and the endothelial derived relaxation factor. Unlike unstable angina where the clot tends to be non-occlusive or only partially occlusive, in acute myocardial infarction the thrombus tends to be totally occlusive. Luminal obstruction results from a combination of the atheromatous plaque, intraluminal thrombus, and a variable degree of coronary vessel spasm. Myocardial infarction is followed by spontaneous lysis of the occlusive clot (referred to as thrombolysis) occurring over a period of hours to days following the infarction. Clot lysis leaves behind a fixed stenosis of varying severity in the culprit coronary vessel. When myocardial necrosis extends from the endocardium to the epicardium, it is referred to as a transmural infarction. When restoration of blood supply

occurs either by natural thrombolysis or with the use of a a drug which achieves the same result, or by means of natural collaterals, the area of injury is restricted to the subendocardial region. This is called a subendocardial or non-transmural infarction.

Microscopic evidence of cellular injury is first seen six to eight hours after the infarction. Infiltration of the injured area with polymorphonuclear cells occurs at about twelve hours and by about twenty-four hours there is evidence of coagulation necrosis and myocyte disruption. Mononuclear cell infiltration and removal of dead myocytes commences around the fourth day, making this period one wherein the infarct is likely to expand or rupture. Deposition of collagen at the periphery of the infarct begins at about ten days and healing with dense scar formation usually requires six weeks.

Clinical features Chest pain is the most common presenting complaint in patients with myocardial infarction. Though the onset of chest pain may be during a period of activity, it commonly commences when the patient is at rest and exhibits a diurnal periodicity occurring more commonly in the morning. The chest pain is characteristically substernal and felt as a sensation of heaviness or squeezing or occasionally it may be described as a crushing sensation. The chest pain may radiate to the arm or to the jaw just like anginal pain but unlike it, is usually more severe, lasts longer than 20–30 minutes and is not relieved by rest or sublingual nitroglycerine. Prominent associated symptoms include profuse sweating, weakness or a feeling of illbeing. When the myocardial infarction occurs in the inferior wall of the left ventricle activation of vagal parasympathetic activity can cause symptoms of nausea, vomiting and abdominal cramps. Syncope or presyncope and bradycardia may be important features in this setting. It must, however, be borne in mind that in 15–20 per cent of patients with acute myocardial infarction, especially in diabetics, there may be a lack of chest pain and the presentation may be with a sudden onset of breathlessness. The clinician should be warned that some patients may experience only non-specific symptoms perceived as a feeling of indigestion.

On physical examination, most patients are anxious, restless and diaphoretic. Tachycardia is common in most patients other than those with inferior wall infarction who may have bradycardia due to vagal reflex stimulation. Auscultation of the precordium may reveal a prominent fourth heart sound. A transient apical systolic murmur, presumably related to mitral regurgitation secondary to papillary muscle ischemia, may be heard. When there is evidence of left ventricular failure, a prominent third heart sound may be heard and examination of the lung fields may reveal bibasilar rales or wheezes.

Investigations The surface electrocardiogram is of primary importance in the diagnosis of acute myocardial infarction (Figs 12.36–12.39). A classic pattern characterised by initial hyperacute T wave peaking followed by ST segment elevation in the leads facing the injured myocardial region develops in more than 70 per cent of patients. The elevation of the ST segment is said to represent transmural myocardial ischemia. As ischemia progresses to cell death, the R wave height is lost and pathologic Q waves (defined as greater than 0.04 seconds in duration and more than 25 per cent of the total QRS height) develop in the leads facing the infarcting area. The ST segment elevation returns towards the baseline over a period of days along with the development of symmetrical T wave inversion. These T wave inversions may persist for weeks or months as may the pathological Q waves. If the ST segment elevation persists late after recovery from myocardial infarction, it may represent an area of aneurysm formation. Fig 12.40 and Table 12.12 depict the localisation of myocardial infarction from the surface electrocardiogram.

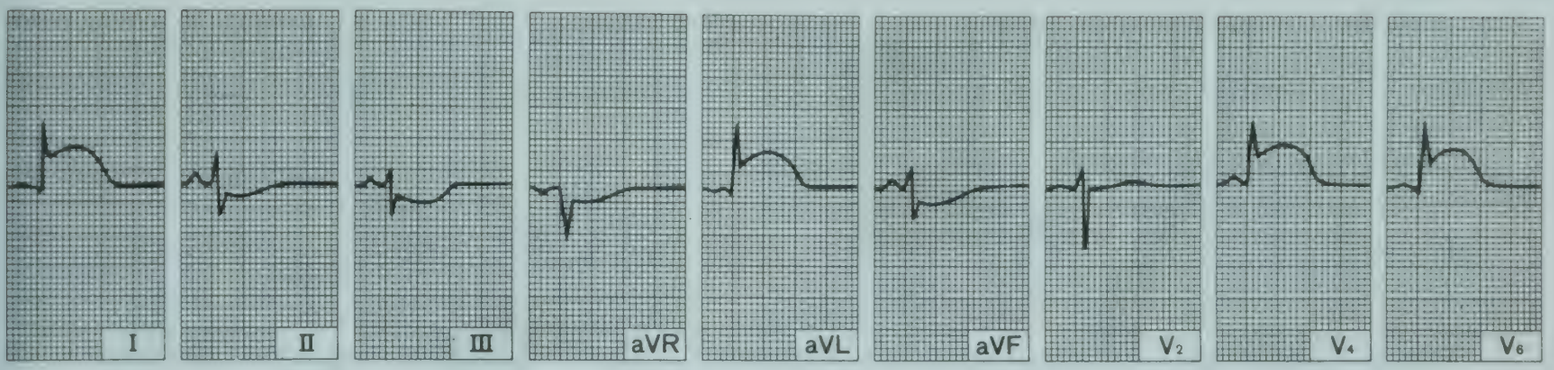


Fig 12.36 Anterior wall infarction: early infarction (hours): ST segment in I, aVL and lateral precordial leads, T depression in II, III, aVF

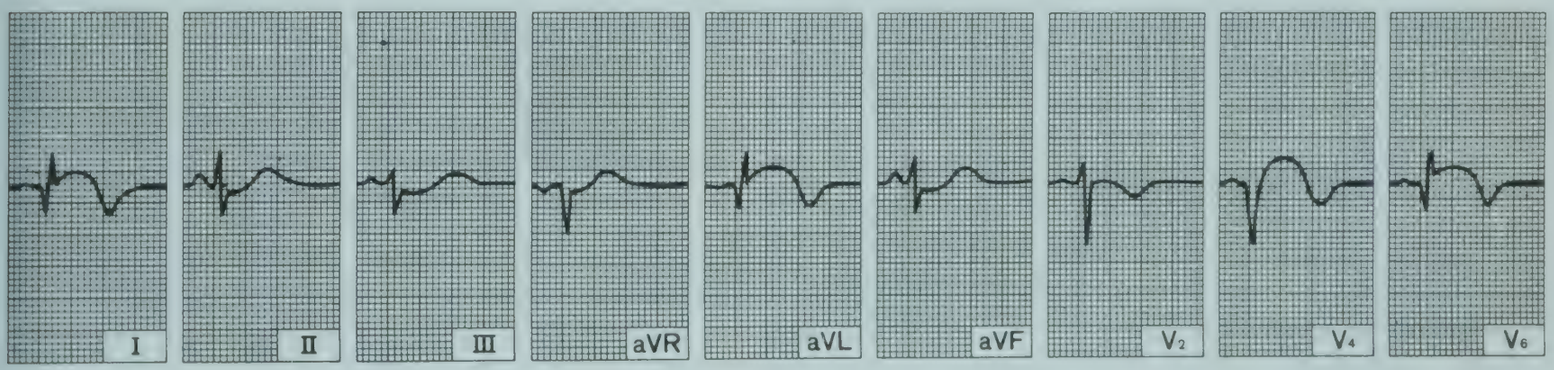


Fig 12.37 Anterior wall infarction: recent infarction (several hours to days): Q wave in I, aVL, and lateral chest leads, QS in V_4, less ST elevation with early T wave inversion

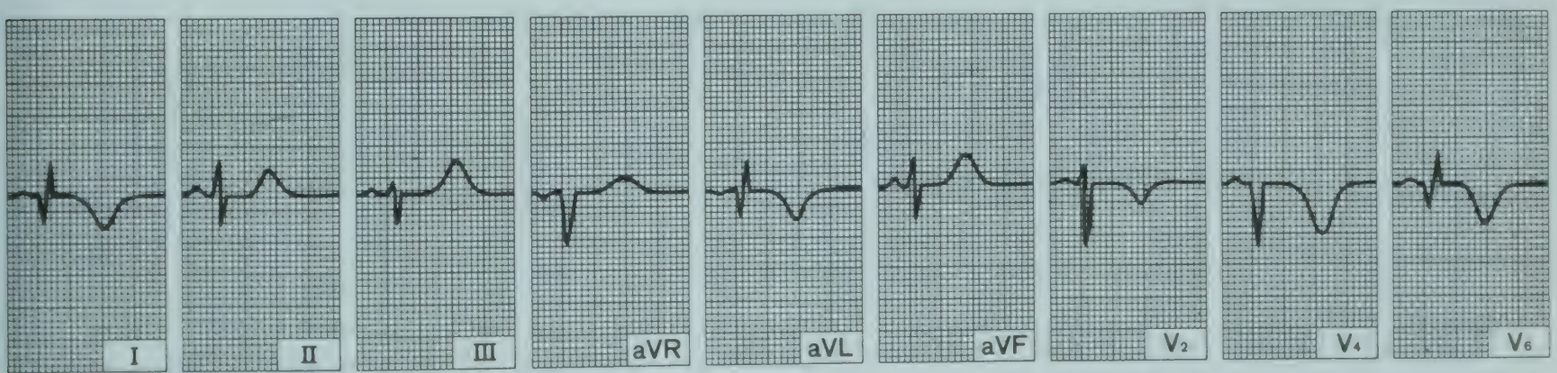


Fig 12.38 Anterior wall infarction: late infarction (days to weeks): ST segments isoelectric, T waves deeply inverted in leads reflecting damaged left ventricle, Q waves essentially as before, QS complexes persist

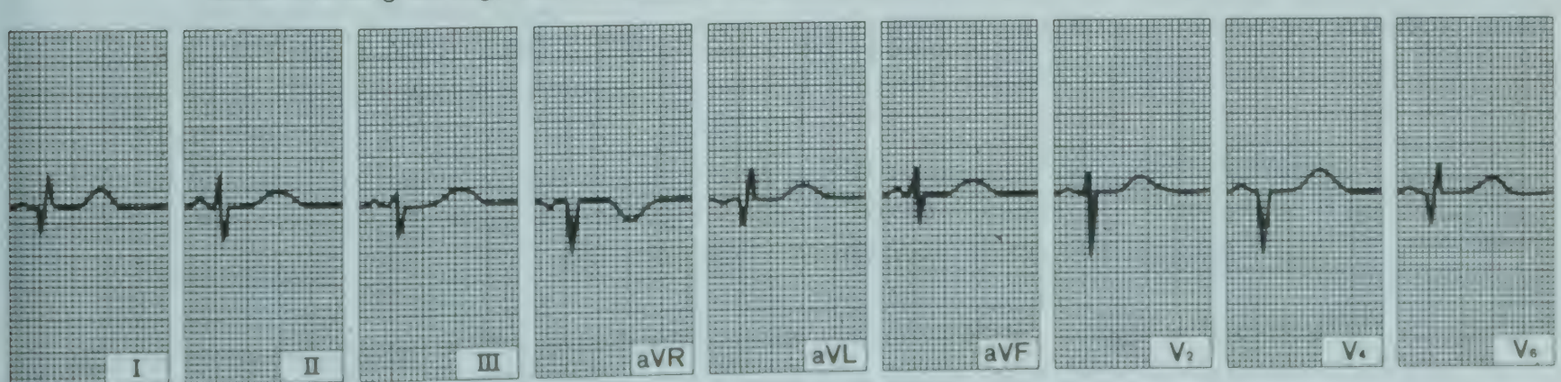


Fig 12.39 Anterior wall infarction: old infarction (months to years): reversion of T waves to normal, fixed abnormal Q waves and QS complexes

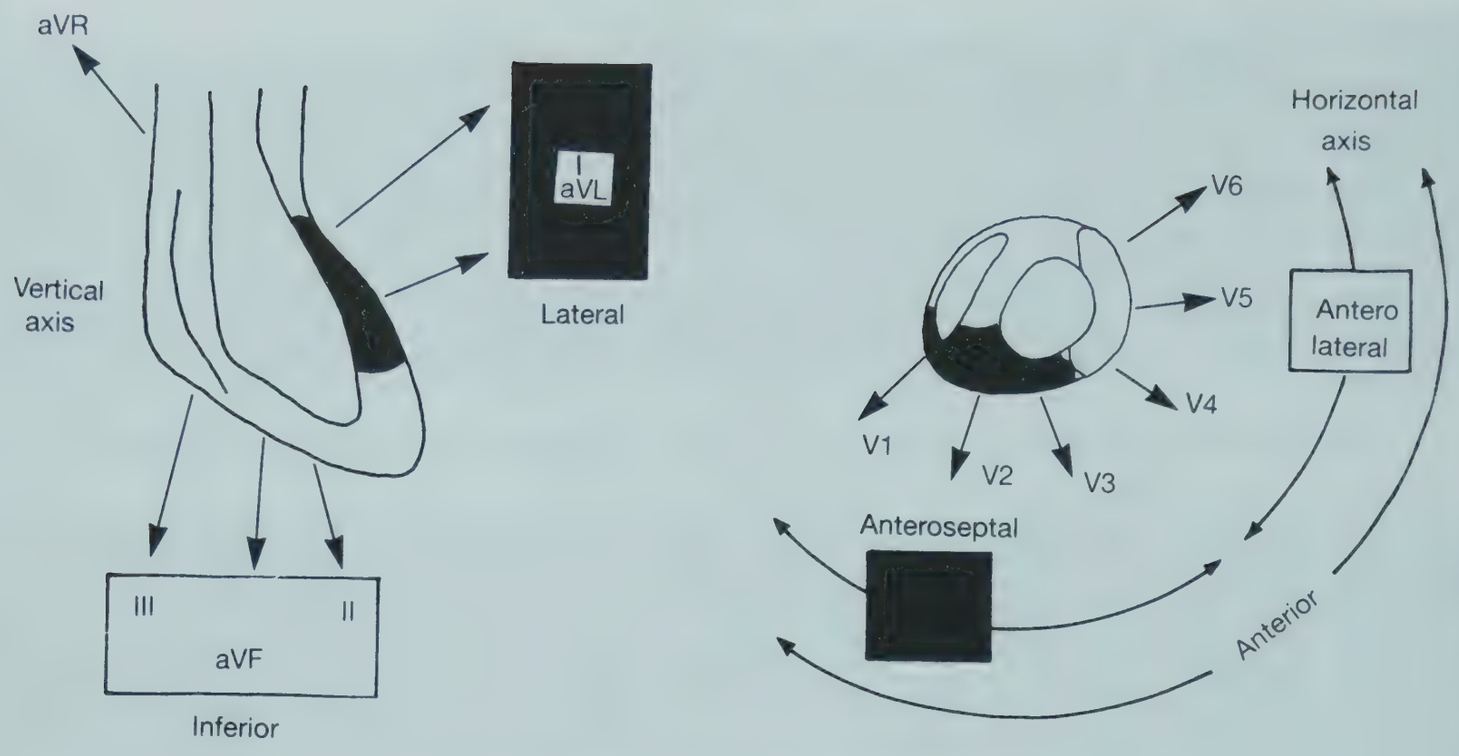


Fig 12.40 ECG localisation of myocardial infarction

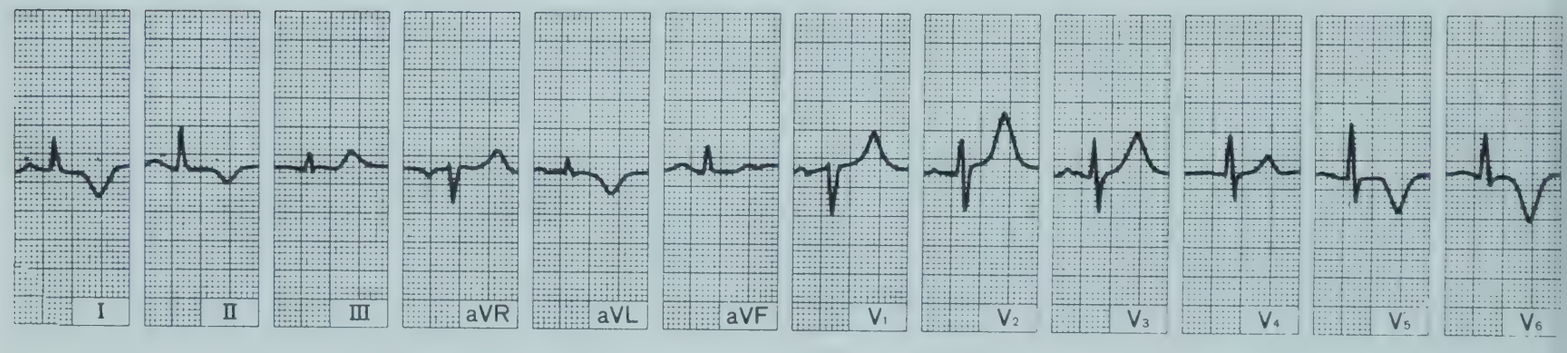


Fig 12.41 Anterior non-Q infarction: deep inverted T waves in I, II, aVL, V_{5-6}, no Q waves are seen

In 30 per cent of cases of acute myocardial infarction, ST segment elevation does not occur. Instead ST segment depression and T wave inversion are present on the initial surface electrocardiogram and persist for over 48 hours or more and are accompanied by biochemical evidence of myocardial necrosis. In these patients Q waves may never develop. This type of infarction is called non-Q wave myocardial infarction (Fig12.41). Though non-Q wave infarctions usually represent non-transmural infarction, it should be borne in mind that the terms Q wave and non-Q wave infarctions are clinical terms whereas transmural and non-transmural infarction are pathological terms. This is essential as there may not be a strict correspondence between the clinical electrocardiogram and the pathological extent of the myocardial infarction. Some patients with acute myocardial infarction and a classic electrocardiogram depicting ST segment elevation also demonstrate depressed ST segments and upright or isoelectric T waves in certain leads remote from the area of infarction. These changes have been labelled *reciprocal changes*. Such reciprocal changes may indicate ischemia at a distance along the territory of a different vessel or they may simply be the result of a mirror effect on the surface electrocardiogram.

Non-specific laboratory abnormalities include the development of mild polymorphonuclear leucocytosis and mild elevation in the erythrocyte sedimentation rate during the first week after myocardial infarction. Such a response seems to be the result of the process of myocardial necrosis. The necrotic cardiac myocytes also release several enzymes into the blood stream; estimation of serum levels of these enzymes is crucial for the diagnosis of myocardial infarction especially when the surface electrocardiogram is non-diagnostic. Creatine phosphokinase (CPK) levels rise within six to eight hours after the onset of infarction, peak at around 24 hours and return to normal by 48–72 hours. Since the CPK enzyme is not specific to the cardiac myocyte, estimation of levels of the specific isoenzyme MB that is found only in the cardiac tissues may be useful. Usually, a relative estimate of the MB isoenzyme and the total creatine phosphokinase provides an estimate of the likelihood of myocardial necrosis. When serum CPK MB levels are more than five per cent of the total CPK levels, myocardial necrosis can be suspected. Total CPK levels can be elevated in various muscular diseases, hypothyroidism following a cerebrovascular accident and even after the administration of an intramuscular injection. Elevation of the MB isoenzyme can also be seen after cardiac surgery, in myocarditis and following electrical cardioversion. If the measurement of CPK or its MB isoenzyme fraction has been missed for some reason, levels of these enzymes may be normal after 48 hours following a myocardial infarction. Under these circumstances, the measurement of serum levels of the enzyme lactate dehydrogenase may be useful as this enzyme rises at around 24–48 hours after infarction, peaks at about three to five days and remains elevated for about 7–10 days. Estimation of the fast-moving LDH-1 isoenzyme provides a more specific indication for myocardial necrosis. The serum aminotransferase enzymes, aspartate aminotransferase, alanine aminotransferase (previously designated as SGPT and SGOT respectively) are non-specific markers of myocyte necrosis; they can be used if facilities for the estimation of CPK or lactate dehydrogenase are unavailable.

A definitive diagnosis of myocardial infarction requires at least two of the following three criteria:

1. a history of characteristic chest discomfort,
2. evolutionary ECG changes, and
3. elevated cardiac enzymes.

When myocardial infarction is clinically suspected but the criteria are not satisfied, acute infarct scintigraphy can be carried out with an infarct avid imaging agent such as ^{99m}technetium pyrophosphate.This infarct avid tracer binds to accumulated calcium within the irreversibly damaged myocardium. Scans are usually positive two to five days after the infarction, sensitivity being highest for transmural infarction and being significantly lower in non-transmural infarction. Where facilities for radionuclide, scintigraphy are unavailable, two-dimensional and Doppler echocardiography can be of considerable value. A regional wall motion abnormality can be demonstrated in nearly all patients with acute myocardial infarction. Echocardiography also provides a non-invasive estimate of left ventricular and right ventricular function, can aid in the diagnosis of right ventricular infarction, can detect ventricular aneurysms or mural thrombi, and can help differentiate the complications of septal rupture or mitral regurgitation, both of which may have clinical evidence of a systolic murmur.

Management of uncomplicated acute myocardial infarction The management of the patient with known or suspected myocardial infarction focuses on early prehospital supportive care, prompt hospital admission and monitoring in the coronary care unit. The introduction of coronary care units in the mid 1960s in the West resulted in a fifty per cent

reduction in mortality associated with acute myocardial infarction.

1. General supportive measures: The patient is kept in the coronary care unit with continuous electrocardiographic monitoring. Adequate intravenous access is established immediately. Visitors are restricted to the minimum to allow the patient to rest. Generally, patients with uncomplicated myocardial infarction spend three to four days in the coronary care unit and are then transferred to an intermediate care unit (also referred to as a step-down unit) with facilities for ambulatory monitoring.
2. Relief of chest pain: Intravenous morphine sulphate administered in a dose of 1–4 mg is the drug of choice for treatment of the pain associated with myocardial infarction. It should be remembered that nausea, vomiting and hypotension are potential adverse effects of morphine sulphate. Nalaxone hydrochloride (an opiate antagonist) should be available if morphine causes respiratory depression. Nitroglycerin can be administered sublingually or in the form of a continuous intravenous infusion for the treatment of the pain. Intravenous administration of beta adrenergic blocking agents may also be helpful for the treatment of the pain of acute myocardial infarction, especially in patients with tachycardia and sympathetic hyperactivity. Oxygen therapy may be useful in subjects with evidence of hypoxemia on the arterial blood gas analysis.
3. Sedation: Administration of a small dose of a benzodiazepine or another anxiolytic agent is beneficial during the initial days following myocardial infarction.
4. Diet and care of the bowels: A low cholesterol liquid or soft diet can be instituted from the first day following myocardial infarction. Since constipation is a common problem, a stool softener or a mild laxative can be administered.
5. Thrombolytic therapy: The treatment of acute myocardial infarction has been revolutionised by the recognition that pharmacologic agents that can lyse the occlusive intraluminal clot in the coronary vessels can significantly restore patency of the affected coronary vessel and thereby reduce the amount of myocardial damage sustained. These pharamacologic agents that can lyse clots are called thrombolytic agents and this therapy is called thrombolytic therapy or reperfusion therapy. Patients who are good candidates for thrombolytic therapy are those who are below the age of seventy-five years, have angina persisting for more than 30 minutes along with new ST segment elevation of at least 1 mm in at least two leads of the surface ECG, and who present within six hours of the onset of chest pain. Absolute contraindications to thrombolytic therapy include a history of recent cerebrovascular accident, major trauma or surgery within the previous eight weeks, active internal bleeding, severe uncontrolled hypertension, active peptic ulcer disease, or a history of prolonged cardiopulmonary resuscitation in the previous two weeks. Relative contraindications to thrombolytic therapy include age of over seventy-five years, history of hemorrhagic diabetic retinopathy or a previous history of peptic ulcer disease. The three thrombolytic agents that have been used are streptokinase, urokinase and tissue plasminogen activator. Streptokinase is usually administered as a continuous intravenous infusion of 1.5 million units administered over a period of one hour. The infusion of streptokinase may be preceded by an injection of intravenous hydrocortisone to counteract any possibility of an allergic reaction. It is the commonest thrombolytic agent used in India. If streptokinase has been administered previously within the last six months, urokinase may be used in a dosage of 1–2 million units infused over one hour by the intravenous route

Both urokinase and streptokinase can result in a systemic lytic state. Tissue plasminogen activator (TPA) and a modified form of streptokinase (anisoylated plasminogen-streptokinase activator complex APSAC) are relatively fibrin specific agents. APSAC has the advantage of being administered as a single bolus of 30 mg with prolonged maintenance of a fibrinolytic state. Tissue plasminogen activator is currently administered by a regimen called front loading; this regimen involves an initial intravenous bolus of 15 mg followed by the administration of 50 mg over a half hour period, followed by the infusion of 35 mg over 60 minutes. Thus, a total dose of 100 mg is administered over 90 minutes. Tissue plasminogen activator is not readily available in our country and is considerably expensive as compared to streptokinase. Clinical trials have demonstrated that all three agents are comparable in their efficacy with a reperfusion rate of 70–80 per cent and a reocclusion rate of 15–20 per cent with a 0.5–1 per cent chance of a major bleeding complications. Thrombolytic therapy salvages ischemic myocardium, reduces infarct size, improves regional and global left ventricular function, promotes remodelling of the damaged myocardium by restoring patency of the supplying vessel, and, importantly, improves survival in patients with acute myocardial infarction. Thrombolytic therapy reduces mortality in acute myocardial infarction by 20–40 per cent depending upon how early it is administered, the maximum benefit being derived when the drugs are given within one to two hours after the onset of chest pain. Some benefits may be accrued in patients with ongoing chest discomfort and ST segment elevation in electrocardiographic leads that do not demonstrate new Q waves even in the time window 6–12 hours after the onset of chest pain. The maximum benefit from thrombolytic therapy seems to be in patients with anterior wall infarction, in hemodynamically complicated infarction, and in the young patient with widespread ECG evidence of myocardium at risk of injury. Patients with inferior myocardial infarction also benefit from thrombolytic therapy. It is now believed that rather than the infarct location, it is the infarct size that is the key variable influencing the benefit from thrombolytic therapy, with no significant benefit in survival being demonstrated in the smallest of infarcts whereas substantial benefit can occur in subjects with large infarcts. The initial acute benefits derived from prompt institution of thrombolytic therapy seemed to be maintained over a long term follow-up period too.

6. Antiplatelet drugs: Major clinical trials have demonstrated that aspirin given alone during the initial phase of acute myocardial infarction substantially reduces mortality. When aspirin is added to streptokinase, an incremental benefit has been demonstrated. It it thus recommended that any patient with acute myocardial infarction be given half a tablet of aspirin sublingually immediately, even before the thrombolytic therapy can be instituted. Subsequently, aspirin should be continued at a dose of 160–325 mg daily provided no contraindications exist.
7. Adjunctive therapy with anticoagulants: It has been suggested that all patients who receive a thrombolytic agent should receive an initial 5000 unit bolus of intravenous heparin followed by a constant infusion of heparin at a dose of 1000 units per hour adjusted to keep the partial thromboplastin time at 1.5–2 times the normal. This is aimed at preventing reocclusion of the coronary artery in which the clot has been lysed. There is some evidence that this practice of administering heparin is critical when TPA is used but less important when streptokinase is used. Once the patient is moved to the intermediate care unit, oral anticoagulants

can be administered especially in subjects with large anterior infarctions or who have symptoms of congestive heart failure. Such therapy with anticoagulants seems to reduce the risk of developing a left ventricular mural thrombus.

8. Beta adrenergic blocking agents: Clinical trials have demonstrated that besides the use of thrombolytic agents, acute administration of beta-blockers by the intravenous route to patients with acute myocardial infarction can limit the infarct size and reduce mortality by a further 20 per cent. Metoprolol given in three doses of 5 mg each at intervals of five minutes may be beneficial and this intravenous doage is followed by an oral dosage of 50–100 mg administered every twelve hours. Patients with a resting heart rate below 50 beats per minute or with a systolic blood pressure less than 95 mmHg, or patients with significant first degree atrioventricular block or advanced atrioventricular block should not receive beta-blockers. Presence of signs of heart failure or an elevated pulmonary artery wedge pressure more than 20–24 mmHg also constitute contraindications to the use of intravenous beta-blocking agents. This acute use of intravenous beta-blockers should be followed up by the routine use of oral beta-blockers for at least two years following the acute myocardial infarction in the absence of contraindications. This long term use of beta-blockers has been demonstrated to reduce the total mortality, reinfarction rate and sudden death rate with benefits being maintained for as long as five years after the episode of acute myocardial infarction.
9. Angiotension-converting enzyme (ACE) inhibitors: There is evidence to suggest that the administration of ACE inhibitors to post-myocardial infarction patients with asymptomatic left ventricular dysfunction (left ventricular ejection fraction ≤ 0.40) prevents the development of heart failure and reduces overall mortality.
10. PTCA: Acute primary PTCA witho preceding thrombolysis has been used as therapeutic strategy in acute myocardi infarction and has been shown to be effecti But this technique is expensive and requir the availability of a 24-hour cardi catheterisation laboratory. This strate however has been shown to be particular beneficial in patients with acute myocardi infarction who are in cardiogenic shock.
11. Calcium channel blockers: There is n evidence to suggest that routine treatme with calcium channel blockers after acu myocardial infarction decreases mortality alters the prognosis favourably. It is therefo not recommended that calcium chann antagonists be administered routinely but th they should be used only if there is a val indication for the use, such as for treatment associated hypertension or in the presence recurrent ischemia.
12. Rehabilitation: Patients with acu myocardial infarction are instructed to mo their toes and feet actively while in bed prevent venous congestion and the possib development of deep venous thrombosis. an uncomplicated myocardial infarction, t patient can be sitting in a chair and feedi within 24 hours of admission. Limited walki under observation can be encourag beginning on the third day after admissi and the patient should be fully ambulato within 5–7 days. The total duration hospitalisation in uncomplicated cases var between 7–10 days. The remainder of t convalescent phase of myocardial infarctio accomplished at home and extends over period of six weeks. During this period, t patient can walk about in the house w periods of rest after the morning a afternoon meals. The patient can return work at the end 6–8 weeks after t myocardial infarction prior to which exercise stress test is often performed.

KEY CONCEPTS

Atherosclerosis

- The atherosclerotic plaque has a necrotic core of extracellular cholesterol and cholesterol esters, cellular debris, and a fibrous cap of collagen, proliferating smooth muscle cells, extracellular and intracellular lipids and foam cells. Atherosclerosis begins in childhood as fatty streaks which are the precursors of fibrous plaques.
- The response to injury hypothesis proposes that endothelial injury results in platelet aggregation, chemotaxis of monocytes, release of growth factors and migration of medial smooth muscle cells into the intima. Oxidative modification of LDL further inhibits the migration of macrophages and stimulates the smooth muscle cells.
- The composition of the cap of the plaque and its morphology are linked to its tendency to fissure, ulcerate or rupture; these complications are the harbinger of major clinical events.
- The non-modifiable risk factors for atherosclerosis include age, male gender, and a family history of atherosclerotic cardiovascular disease. Modifiable risk factors include hypertension, dyslipidemias (increased LDL, and triglycerides and low HDL), smoking, obesity, diabetes, physical inactivity and increased left ventricular mass. The newer risk factors include elevated fibrinogen and homocysteine levels, and insulin resistance.

Angina pectoris

- Angina refers to episodes of chest heaviness (tightness/uneasiness/suffocation) that are brought on by exertion, relieved by rest (or nitroglycerin) and which may radiate to the arms, necks or the jaws. An episode usually lasts between 5–15 minutes.
- The pathophysiologic basis of angina is increased myocardial oxygen demand relative to the supply. In most patients angina is due to critical atherosclerotic narrowing of one or more segments of the epicardial coronary arteries.
- The ischemic cascade consists initially of accumulation of ischemic metabolites (lactate), which is followed sequentially by electrocardiographic abnormalities, and reduced ventricular diastolic and systolic function.
- Physical examination of a patient during an anginal attack may reveal (besides an elevated double product [hr x BP]) a dyskinetic apex, an S_4, or a transient systolic murmur of papillary muscle dysfunction. An ECG obtained during the episode of angina provides confirmatory evidence if it reveals ischemic ST-T changes.
- An exercise stress test (usually obtained on a treadmill) is useful for diagnosis (70% sensitivity and 90% specificity) and for risk stratification. The diagnostic utility of a stress test is limited in an asymptomatic individual, a young subject, or a premenopausal female (low pretest probability).
- A thallium (Tl^{201}) perfusion scan enhances sensitivity (80%) while maintaining specificity; areas of ischemia appear as cold areas that undergo redistribution on delayed imaging. SPECT thallium scan further enhances the accuracy of the perfusion scan. Dipyridamole-thallium scan or dobutamine-echocardiogram are alternatives for diagnostic testing in patients who cannot exercise adequately. The gold standard for diagnosis of atherosclerotic coronary artery disease is coronary angiography: a stenosis >70% of luminal diameter is considered to be hemodynamically significant.
- Medical management of angina includes risk factor management (control of blood pressure, lipids, dietary modifications, cessation of smoking, weight loss [for obese patients]), and treatment of the chest pain. Angina is managed effectively with long acting nitrates for prophylaxis of attacks (allowing nitrate-free intervals to obviate tolerance), sublingual nitrolycerin for the acute attack, and betablocking drugs or calcium channel antagonists (for prophylaxis) along with antiplatelet drugs (aspirin).
- Triage for surgery is often based on the coronary anatomy, response to medical treatment and individual patient preferences. Surgical coronary artery bypass grafting (CABG: 1% operative mortality) is the recommended treatment for patients with left main coronary artery disease, with triple vessel disease with left ventricular dysfunction, and with triple vessel disease with normal ventricular function if the proximal left anterior descending artery is involved. Percutaneous transluminal coronary angioplasty (PTCA) is often preferred if there is single or double vessel disease with discrete stenosis (an ideal lesion is also concentric, and non-calcific; success rate of over 90%; 1% mortality and 33% restenosis over 6 months).

Unstable angina

- Unstable angina includes 4 subsets: new-onset angina, crescendo angina, rest angina, and post-MI angina.
- The underlying pathology in unstable angina is an eccentric plaque which is fissured and has a superimposed non-occlusive thrombus.

- The diagnosis is based on history; unlike the usual anginal episodes, the chest pain in unstable angina tends to be more prolonged and also more intense.
- The patient is usually admitted to a CCU to exclude an MI; ECG shows ischemic ST-T changes that tend to be reversible. Serial enzymes (CPK/CPK MB) are usually within the normal range. These features distinguish it from a non-Q wave MI.
- The treatment consists of bed rest, aspirin, intravenous heparin, nitrates (oral/intravenous), and anti-ischemic drugs (beta-blockers and calcium channel blockers).
- After stabilisation, patients who have had unstable angina may merit coronary angiography for facilitating further clinical decision making.

Acute myocardial infarction

- MI refers to ischemic myocardial necrosis, which is usually due to occlusive thrombosis superimposed on an atherosclerotic plaque in an epicardial coronary artery.
- MI presents with severe, prolonged (>30 minutes) retrosternal chest pain which is unrelieved by nitroglycerin. Pain typically radiates to the arm or the jaw and may be associated with sweating, shortness of breath, nausea and vomiting.
- Physical findings include marked apprehension, tachycardia, palpable dyskinetic apical ventricular segment and an audible S4. A transient systolic murmur of papillary muscle dysfunction or a pericardial friction rub may also be heard if carefully sought.
- Some potential complications include arrhythmias, infarct expansion, with tamponade, and pericarditis (early and delayed).
- Pathologically, an MI may be transmural (involving the whole thickness of the myocardium; usually with Q waves in the ECG) or non-transmural (subendocardial; no Q waves in the ECG). Since the anatomic extent of necrosis does not correlate with ECG presence or absence of Q waves, a classification based on ECG alone (Q wave MI: deep Q waves, ST segment elevation; non-Q wave MI: no Q waves on ECG but with persistent non-resolving ST segment depression and T wave inversions) is preferred.
- The diagnosis of MI is based on presence of two of three positive findings: clinical picture, ECG changes (sequential changes: hyperacute T wave peaking followed by ST segment elevation, and T wave inversion and appearance of q waves), and serum levels of certain enzymes indicating myocardial necrosis.
- ECG changes in leads V_1–V_6 indicate anterior infarction; changes in V_1–V_3 indicate anteroseptal MI; changes in II, III, aV_F indicate inferior MI; changes in I, aVL, V_5–V_6 indicate a lateral wall MI. A feature suggestive of a posterior wall MI is an R wave greater than the S wave in V_1. Right ventricular MI is diagnosed by demonstrating ST segment elevation in right precordial leads. Atrial infarction is suspected if there are changes in the P wave morphology, depression of the PQ segment or atrial arrhythmias.
- Of the serum enzymes, CPK levels begin to rise within 6 hours, peak at 18 hours, and normalise by 72 hours; elevation of the CPK MB isoenzyme is more specific. LDH levels begin to rise at 24 hours, peak at 48–72 hours and normalise in 10–14 days; LDH 1 isoenzyme is more specific.
- Non-specific markers of myocardial necrosis include an elevated ESR (usually after 48 hours) and leucocytosis (usually commencing within 24 hours and lasting about 10 days). A nuclear technetium pyrophosphate (PyP) scan is helpful for the diagnosis of MI if the enzymes are equivocal, and in post-surgery patients (in whom enzymes are not a reliable index); an area of infarction appears as a hot spot.
- A patient with MI is best managed in a coronary care unit (CCU). Vital signs are assessed, and the ECG is continuously monitored. Oxygen inhalation is instituted if the patient is hypoxemic. Relief of chest pain may be obtained with i.v. morphine or nitroglycerin. Aspirin may be administered (to be chewed) immediately. Thrombolysis should be initiated in patients with Q wave MI who present within 6 hours of chest pain if there is no contraindication (contraindications include prolonged CPR, major bleeding tendency or history in the past, severe uncontrolled hypertension, recent major surgery). The thrombolytic agents include streptokinase, tissue plasminogen activator and APSAC; these agents have approximately similar efficacy. Thrombolysis reduces infarct size, improves residual left ventricular function and reduces short-term and long-term mortality.
- Intravenous beta-blocking agents should be administered initially and this is followed by oral beta-blockers unless there is a specific contraindication (severe CHF, severe bradycardia [heart block]). These agents also reduce infarct size, and overall short-term and long-term mortality (including sudden cardiac death).
- It is currently recommended that converting enzyme inhibitors be started in patients with large anterior infarctions, especially if the LV ejection fraction is less than 0.40.

- General supportive measures include institution of a soft diet, stool softener, and mild sedative (if required). Most uncomplicated MI patients can be moved to a step-down unit by 3–4 days and can be discharged from hospital by 8–10 days.
- The important components of care after discharge include rehabilitation, gradual resumption of physical activities, management of risk factors (smoking cessation, lipids, diabetes, obesity) and a treadmill exercise stress test for risk stratification. Beta-blocking drugs, antiplatelet agents and converting enzyme inhibitors are continued.

12.7 Cardiac arrhythmias

Conduction of the normal cardiac impulse

The normal cardiac impulse (Fig 12.42) originates in the sinus node and travels rapidly across the atria over three atrial bundles (internodal pathways) to the atrioventricular (AV) node. The major delay in conduction of the impulse from the atria to the ventricles takes place at the level of the AV node (about 40 msecs). From the AV node, the impulse propagates through the bundle of His and is then conducted rapidly along the right and left bundle branches to activate the ventricles by way of the network of Purkinje fibres. The right bundle branch is relatively thin as compared to the left bundle and traverses the right side of the anterior interventricular septum from the bifurcation of the common bundle into the right ventricle. The left bundle divides into two branches: an anterior (superior) fascicle, which runs along the left side of the interventricular septum to activate the anterior left ventricle, and a larger posterior (inferior) fascicle, which dips dorsally and fans out to activate the posterior septum and the posterolateral left ventricular wall.

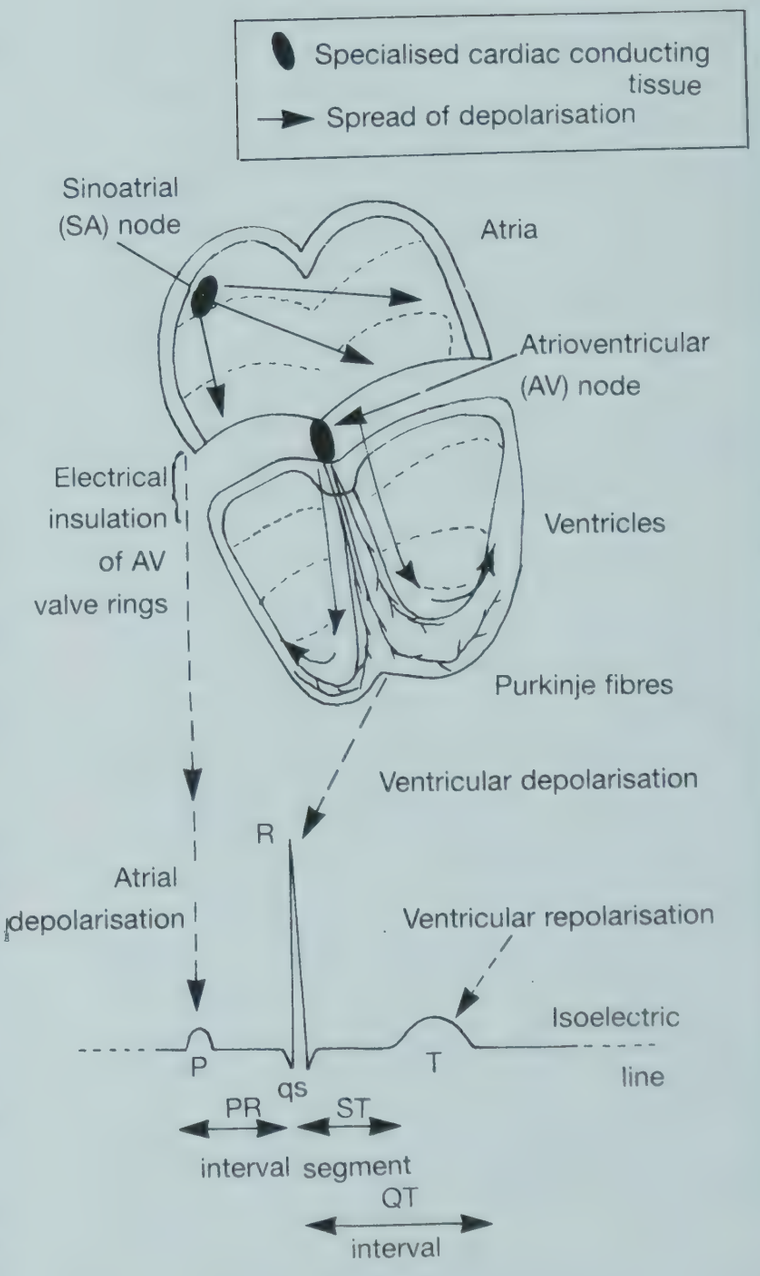


Fig 12.42 Spread of depolarisation through the heart and associated changes in the electrocardiogram

Classification of arrhythmias

Disturbances of cardiac rhythm can be broadly classified into three categories: passive arrhythmias, automatic or ectopic arrhythmias, and reentrant arrhythmias. *Passive arrhythmias* occur when the automaticity, excitability, and conduction properties of the pacemaker or the conduction system become depressed. They are manifested as bradyarrhythmias and as

disturbances of atrioventricular (AV) and intraventricular (IV) conduction. *Automatic or ectopic arrhythmias* result from enhanced automaticity of an ectopic focus (residing in the atria, the AV node and junction, or the ventricular His-Purkinje system) which begins to act as a pacemaker by virtue of its capability of undergoing spontaneous diastolic depolarisation. *Reentrant arrhythmias,* which account for the majority of premature beats and tachyarrhythmias, occur when there are two pathways of impulse conduction with differing electrical characteristics. One pathway carries the impulse forward (antegrade) and the other conducts the reentering impulse backward (retrograde). The recovery of excitability proximal and distal to the reentry sites allows the establishment of a reentrant circuit. *Triggered activity* is the fourth mechanism for the origin of cardiac arrhythmias the importance of which is not fully clear at present. Triggered activity may be defined as repetitive electrical activity arising from delayed after depolarisations. This is the mechanism of origin of some digitalis-induced arrhythmias.

General Approach to the Patient with Arrhythmias

Physical examination may yield important information regarding an arrhythmia. The jugular veins must be examined for cannon waves, and the peripheral pulse examined for any pulse deficit; fluctuations of systolic blood pressure and heart sounds should be specifically sought. AV dissociation is characteristic of ventricular tachycardia; it is characterised by intermittent cannon waves in the jugular veins, fluctuation in the systolic blood pressure, marked variation in the intensity of heart sounds, and intermittent third and fourth heart sounds. In contrast, paroxysmal supraventricular tachycardia is characterised by monotonously uniform but rapid heart sounds. The response to careful carotid sinus massage may yield additional clues besides helping to terminate certain arrhythmias (see below).

The ECG must be examined with the following five basic questions in mind: 1) Are P waves present or is there any other evidence of atrial activity, such as flutter waves or fibrillatory waves? 2) What is the relation between the atrial activity and the QRS complexes? 3) Are the QRS complexes wide or narrow (that is, greater than or less than 0.10 second)? 4) Is the ventricular rhythm regular or irregular? 5) Are any early beats or pauses observed?

On the regular 12-lead electrocardiogram, atrial activity is usually seen most clearly in leads II, III, aVF, or V_1. Special leads, such as the CR lead,[1] may show P waves better. Esophageal leads or intracardiac recordings provide much clearer evidence of atrial activity than the surface and may need to be used occasionally.

ATRIAL TACHYARRHYTHMIAS

Paroxysmal Supraventricular Tachycardia (PSVT)

ECG recognition (Fig 12.43) This is an atrial tachycardia with a rate of 150–250 beats/minute with narrow normal-looking QRS complexes and P waves which can precede or follow the QRS complexes, or occasionally be invisible (when buried in the QRS complex).

Electrophysiology Reentry accounts for 95 per cent of SVTs, with *enhanced automaticity* being the underlying mechanism for the remaining 5 per cent. Of the reentrant SVTs, three-fourths are due to *AV nodal reentry* and the rest are due to an *accessory pathway* (see preexcitation syndromes), *sinus node reentry* or *intraatrial reentry.* AV nodal reentry is characterised by retrograde P waves,[2] most frequently buried in the QRS complex; intraatrial reentry by

[1] In the CR lead, the right arm electrode becomes an indifferent electrode, and the left arm electrode is used as an exploring precordial electrode while the electrocardiogram is recorded on lead I.

[2] Retrograde meaning P wave following the QRS as atrial activation is retrograde, almost simultaneous with ventricular activation

antegrade P waves which precede the QRS (reflecting an anterograde atrial activation sequence); and sinus node reentry by P waves morphologically identical to the sinus rhythm. In automatic, atrial tachycardias, P wave morphology depends on location of the ectopic pacemaker.

AV nodal reentry is characterised by *longitudinal dissociation* of the AV node into two functionally distinct pathways, designated *alpha* and *beta*. The alpha pathway is slow-conducting but its refractory period is shorter than the faster conducting beta pathway. Atrial premature beats which are early can block the beta pathway, conduct antegrade slowly over the alpha pathway and find the beta pathway available for retrograde conduction. After rapid beta pathway conduction the impulse may find the alpha pathway available again (due to its short refractory period) for antegrade conduction, thereby setting off a circus movement tachycardia (Fig 12.24).

The underlying atrial mechanism determines the response of the tachycardia to vagal tone enhancement maneuvers, with reentrant tachycardias being slowed or terminated and automatic tachycardias remaining unaffected.

Clinical features PSVT occurs in persons of all ages. Although it is most often seen in young subjects without any underlying disease, the arrhythmia has been associated with rheumatic, atherosclerotic, hypertensive or thyrotoxic heart disease. It may be precipitated by emotional stress, physical fatigue or by the excessive use of tobacco, coffee, or alcoholic beverages.

Episodes of PSVT have a sudden onset and termination. The principal symptoms are those of palpitations or chest uneasiness. Most patients tolerate the arrhythmia very well. Some patients mention the presence of precordial pain, weakness, nausea, and even syncope. Some patients with underlying hypertensive heart disease or coronary artery disease may develop symptoms of pulmonary congestion.

Treatment An acute attack of PSVT may be terminated by vagal maneuvers such as carotid sinus massage or the Valsalva maneuver[1]. Pharmacologic conversion can be achieved using several agents. Adenosine (6 mg i.v. over 2 seconds), if available, has emerged as the drug of choice for PSVT. A second dose (12 mg over 2 seconds) may be used if there is no response to the first dose in 2–3 minutes. Esmolol (100 µg/kg/min), a short-acting beta-blocker, may also be tried if available. Intravenous verapamil, 5 to 10 mg by bolus injection, is an excellent drug for a narrow QRS tachycardia. If verapamil is unavailable, the following agents

[1] Carotid massage should be performed cautiously. Other vagal maneuvres such as eyeball pressure or 'diving' reflex (facial immersion in cold water for 5–10 sec) are uncomfortable to the patient.

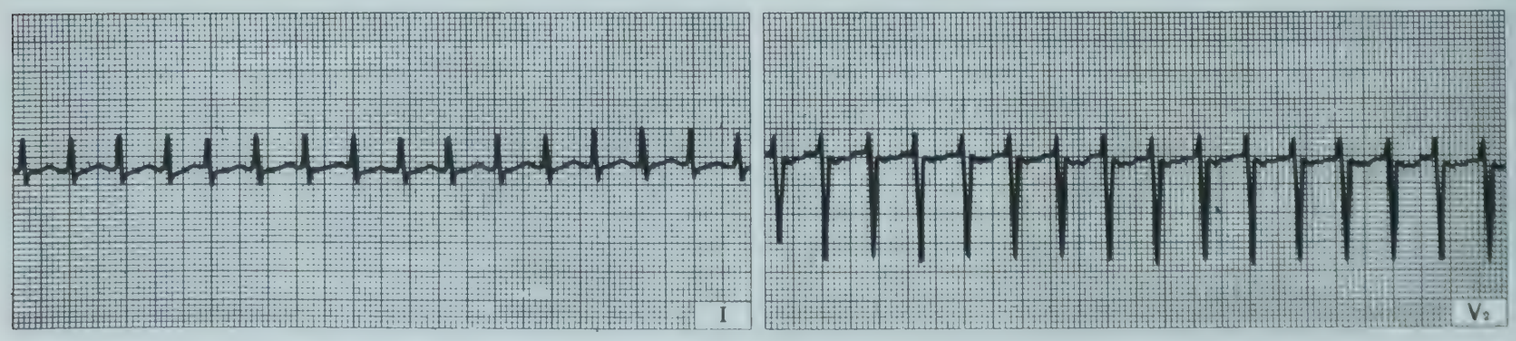


Fig 12.43 Paroxysmal atrial tachycardia : ectopic atrial focus (buried P waves in I, present in V2), rhythm regular, may show minor ST segment depressions in precordial leads

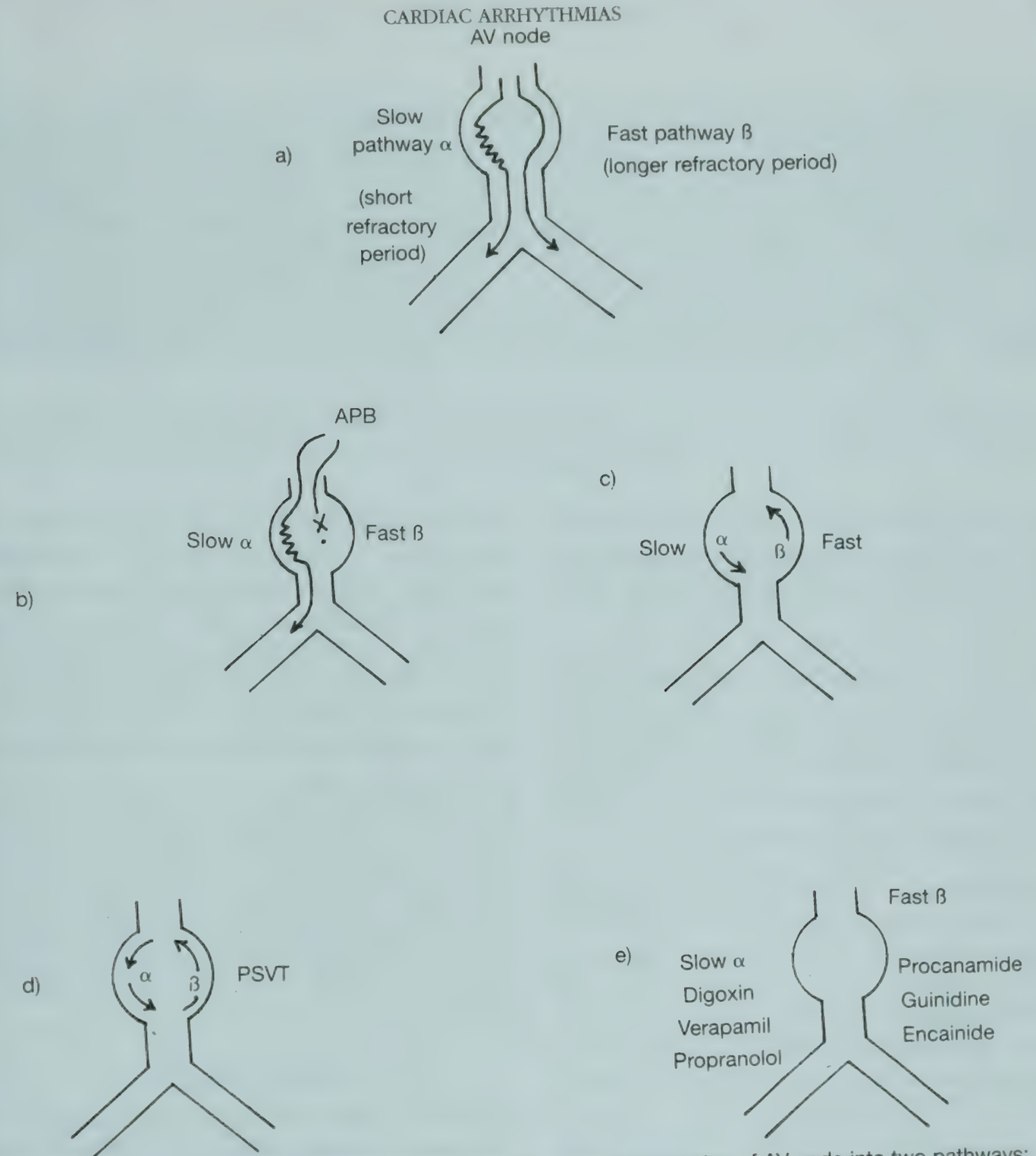


Fig 12.44 Electrophysiology of AV nodal reentry: a) functional dissociation of AV node into two pathways; b) atrial premature beat (APB) blocks the β path and conducts along the α pathway; c) retrograde conductions along β pathway; d) reentrant 'circus' movement sets off a tachycardia; e) drugs affecting the slow and fast pathways

may also be used: propranolol (1 mg i.v. every 5 minutes to a maximum dose of 0.1 mg/kg), digoxin (0.5–1 mg i.v.), or edrophonium (10 mg i.v. bolus). If pharmacologic means are unsuccessful, electrical cardioversion (DC countershock of 50–200 watt-sec) may be used.

For patients with frequent recurrent PSVT episodes, several medications appear to be of prophylactic benefit. Oral verapamil (180–240 mg/d), digoxin, or propranolol are all effective.

Atrial Flutter

ECG recognition (Fig 12.45) Atrial flutter is an atrial tachycardia characterised by a constant atrial rate of 250–350 beats/minute. This atrial activity appears as coarse, saw-tooth undulations

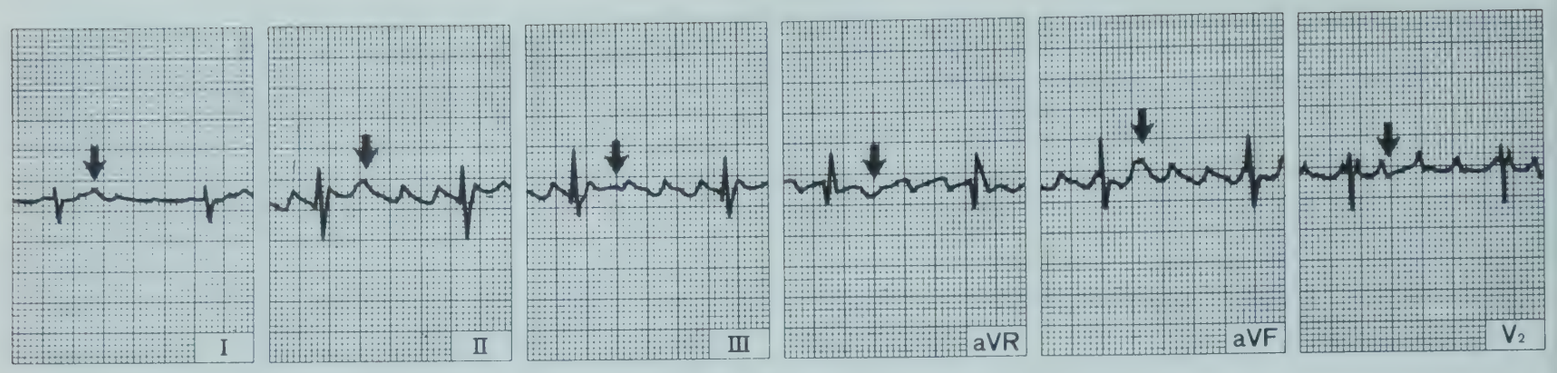


Fig 12.45 Atrial flutter: saw-tooth flutter waves may occur at rates of 220–350 per minute, saw-tooth flutter waves seen in II, III, aVF, regular atrial rhythm (4:1 ventricular response), second flutter wave (indicated by arrows) altered by superimposition on T wave

of the baseline (*F waves*) best seen in leads II, III, AvF and V_1. The ventricular rate is regular and half, one-third or one-fourth of the atrial rate.

Etiology Atrial flutter may occur as part of a 'sick sinus syndrome' or may be secondary to organic heart disease (coronary artery disease, myocardial disease, mitral valve disease), alcohol intake, thyrotoxicosis or chronic obstructive pulmonary disease.

Electrophysiology Atrial flutter is mostly due to intraatrial reentry of flutter wavelets that encounter areas of inhomogeneous refractoriness (the substrate for reentry). Since the AV node cannot usually conduct at a rate of 250–350 minute, atrial flutter is usually associated with varying degrees of atrioventricular (AV) block (commonly 2:1 AV block).

Vagal maneuvers like carotid sinus massage are helpful in the diagnosis of atrial flutter by increasing the degree of AV block, slowing the ventricular response and revealing the flutter waves on the ECG. The response is often *abrupt* with a prompt return of the original ventricular rate after cessation of the maneuver.

Treatment If the patient is hemodynamically compromised, electrical cardioversion should be performed usually with an energy of 20 watt seconds.[1]

[1] 1 watt second = 1 joule of energy

If the patient is stable and is tolerating the arrhythmia, pharmacologic reversion, sometimes called *pharmacologic cardioversion,* may be attempted with *class IA* drugs (quinidine, procainamide, diisopyramide, see Table 12.23). It should be borne in mind that as the flutter rate drops, 1:1 AV conductions may become possible with a consequent acceleration of ventricular response that can be clinically deleterious. Hence these agents should be used after the ventricular rate has been controlled with *drugs that block* the AV node (digitalis, verapamil, propranolol). With digitalis alone which shortens atrial repolarisation, about fifty per cent of patients with atrial flutter convert to atrial fibrillation.

Atrial Fibrillation

ECG recognition Atrial fibrillation is an atrial tachycardia with an atrial rate of 350–450 beats/minute. This rate is so fast that discrete atrial activity may not be discernible on the ECG (*fine fibrillation*). Occasionally coarse irregular 'fibrillary' waves may be seen (*coarse fibrillation*). The ventricular rate is totally irregular (Fig 12.46).

Etiology Atrial fibrillation may be acute or chronic. Chronic atrial fibrillation is often associated with organic heart disease due to coronary disease, myocardial disease, pericardial disease, hyperthyroidism and mitral valve

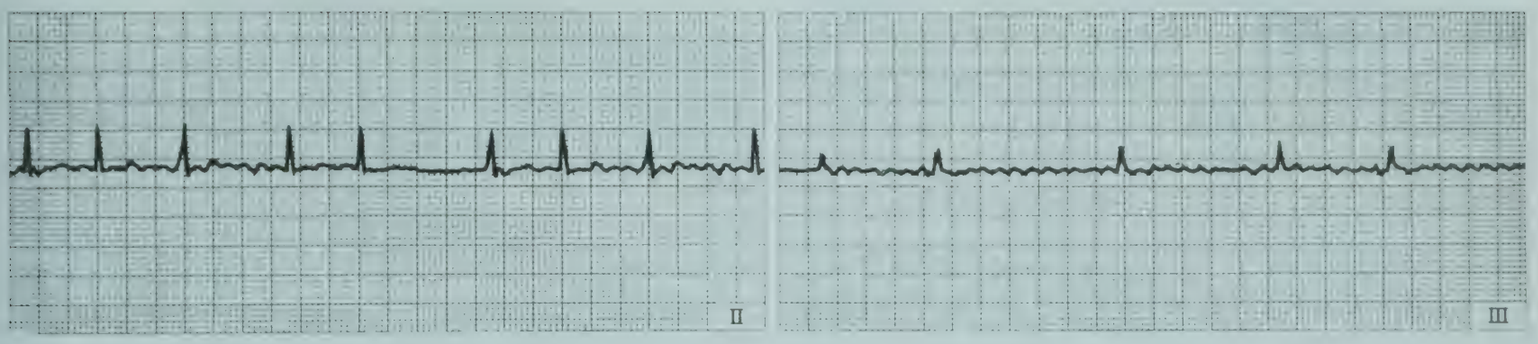


Fig 12.46 Atrial fibrillation: asynchronous atrial contractions, rapid, irregular f waves, totally irregular ventricular response

disease. It may, however, be present without a demonstrable etiology and is then known as *lone atrial fibrillation.* Acute onset atrial fibrillation may be seen in acute myocardial infarction (especially with atrial infarction), pulmonary embolism, chronic obstructive airway disease with acute exacerbation, alcohol ingestion or in the presence of preexcitation syndromes.

Electrophysiology Atrial flutter and fibrillation are probably part of a spectrum of intraatrial re-entry. When flutter wavelets encounter areas of inhomogeneous refractoriness they break into secondary wavelets and multiple areas of re-entry. This produces a totally chaotic atrial rate. The ventricular rate is irregularly irregular (resulting in irregular R-R intervals) as only a fraction of the atrial impulses that reach the AV node are transmitted to the ventricles. For the impulses that do conduct, the QRS and T waves are normal. The average ventricular response to atrial fibrillation among patients not receiving beta-blockers or digitalis is 140–160 beats/minute. A ventricular response less than 100 beats/minute in an untreated patient indicates underlying disease in AV conduction. A ventricular response more than 180 beats/minute may indicate underlying thyrotoxicosis, dyselectrolytemia (hypokalemia or hypomagnesemia), effect of sympathomimetic drugs or a preexcitation syndrome. In preexcitation syndromes a rapid irregular wide complex tachycardia is observed (see below).

Pathophysiology Disorganised atrial activity leads to a reduction in cardiac output due to loss of an 'atrial kick' in ventricular diastolic filling. The rapid ventricular rate leads to a reduction in diastolic filling which may further reduce cardiac output due to reduced diastolic filling. Prolonged periods of atrial fibrillation are associated with stasis in atrial appendages and eventually with the development of atrial thrombi. These atrial thrombi have embolic potential — systemic emboli (from left atrium) and less commonly pulmonary emboli (from right atrium).

Treatment If the arrhythmia is poorly tolerated hemodynamically, electrical cardioversion can be attempted. When the patient is hemodynamically stable the choice of treatment depends on the absence or presence of underlying left ventricular dysfunction. If it occurs without an underlying disease, class IA drugs are effective in 30–50 per cent of patients. In the presence of congestive heart failure, chronic arrhythmia (>6 months) and enlarged left atrium (>4.5 cm by echocardiogram), the aim is to control ventricular response since restoration of the sinus rhythm is less likely. Digoxin, verapamil or propranolol may be used alone or in combination. Therapy can be initiated with digoxin and verapamil or propranolol can be added subsequently to maintain a ventricular rate of 70–80 beats/minute at rest.

Oral anticoagulation is advised for patients with concomitant mitral valve disease, cardiomyopathy and even in lone atrial fibrillation (due to risk of stroke).

Multifocal Atrial Tachycardia (MAT)

ECG recognition In this tachyarrhythmia, there are discrete P waves of at least three separate morphologies and there is an atrial rate greater that 100 beats/minute with irregular P-P intervals. Non-conducted P waves and varying P-R intervals are common. When the atrial rate is less than 100 beats/minutes but other morphologic characteristics are the same, the term *chaotic atrial mechanism* is used.

Etiology This tachyarrhythmia is seen especially in association with decompensated chronic obstructive pulmonary disease and in severe congestive failure. Bronchodilators, dyselectrolytemia or metabolic imbalances all serve to exacerbate this condition.

Treatment The treatment of MAT is treatment of the underlying pulmonary disease with relief of hypoxemia and hypercarbia. Digitalis is rarely helpful and may, in fact, exacerbate the tachyarrhythmia.

Preexcitation Syndromes

ECG recognition Pre-excitation syndromes are conditions wherein there is ECG evidence of accelerated transmission of impulses from the atrium to the ventricles via the *accessory pathways,*[1] (that bypass the normal physiologic delay in the AV node) alongwith clinical symptoms. The exact ECG features depend on the location of these *bypass tracts.* In the *Wolff-Parkinson-White* syndrome, an accessory *bundle of Kent* extends from the atrium to the His-Purkinje system. The sinus impulse conducts through both the AV node and the accessory pathway (Fig 12.47). The P-R interval is short as the accessory tract conducts faster than the AV node. The QRS is a widened *fusion complex*: an initial early depolarisation via the fast Kent bundle causes a slurred upstroke (the '*delta wave*') followed by a late ventricular depolarisation that occurs over the normal His-Purkinje system. In the Lown-Ganong-Levine (LGL) syndrome, an accessory pathway extends from the atrium to the AV node. The ECG hallmark is a short PR interval with a normal QRS complex.

[1] Also called 'anomalous connections'

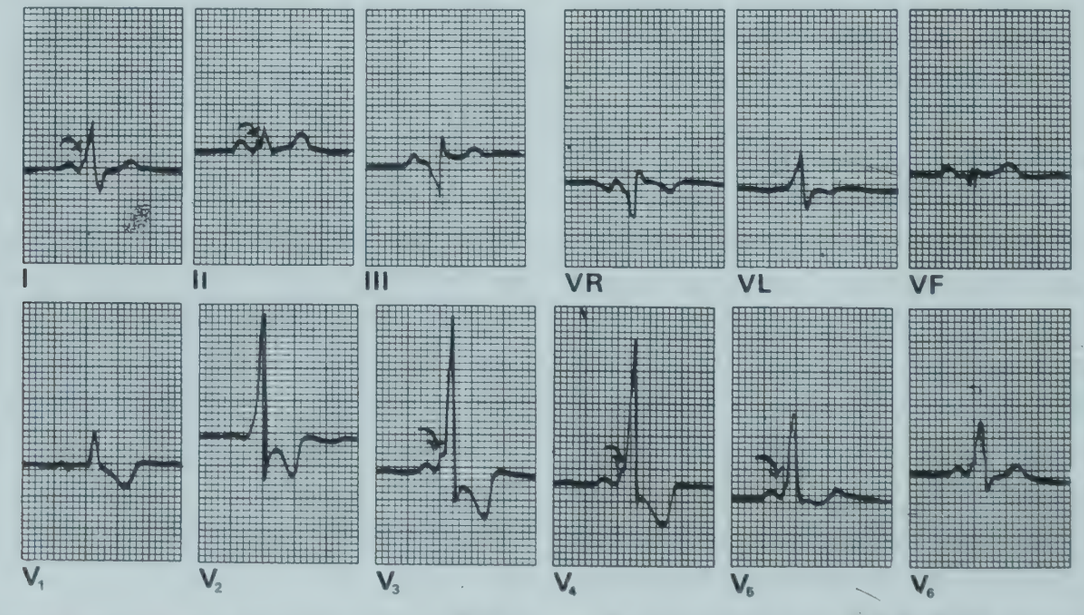


Fig 12.47 Wolff-Parkinson-White syndrome: note the short P-R interval, the wide QRS. The upstroke of R in leads I, II, aVL, V_{2-6} is slurred by the delta wave (arrow). Also note the ST segment depression V_{2-5} and T wave inversion in leads aVL, V_{1-4}

Etiology Preexcitation syndromes are due to congenital bypass tracts usually (in 66%) in the absence of other organic heart disease. There is an important association with Ebstein's anomaly[1] of the tricuspid valve, mitral value prolapse and cardiomyopathies.

Electrophysiology (Fig 12.48) In contrast to the AV node, the accessory paths do not demonstrate decremental conduction.[2] The accessory pathway serves therefore, as a substrate for conducting retrogradely, thereby triggering a 'cirus movement' (reentrant circuit). The most common arrhythmia is a supraventricular tachycardia with anterograde conduction over the AV node and retrograde conduction over the accessory pathway (*orthodromic tachycardia*). In this situation, the QRS complex appears to be narrow as the ventricular activation sequence is normal. Since the atria are activated retrogradely through the accessory pathway, P waves immediately follow the QRS complex. Further, since most of the accessory pathways in these patients are left-sided, atrial activation occurs from left to right manifesting in the ECG as negative P waves in lead I (b). In rare cases, supraventricular tachycardia occurs with antegrade conduction over the accessory pathway and with a retrograde conduction over the AV node (*antidromic tachycardia*). Since the ventricle is exclusively activated by the accessory pathway, there is a wide QRS tachycardia (c). This has to be differentiated from ventricular tachycardia.

In the older WPW syndrome patients, the onset of atrial fibrillation is particularly catastrophic as the rapid conduction over the accessory pathway leads to a rapid ventricular rate that can degenerate into ventricular fibrillation leading to sudden death. Paroxysmal atrial fibrillation occurs in 15–20 per cent patients with WPW syndrome.

Treatment The asymptomatic patient with WPW syndrome requires no treatment. Exercise testing has been used in these patients to identify a subset of patients who have a short anterograde refractory period of the accessory pathway. Such patients show progressive preexcitation with maximal heart rates and it is likely that hemodynamic collapse will occur if atrial fibrillation develops.

Treatment of the symptomatic patients is guided by the clinical condition of the patient, the rate of the tachyarrhythmia and the nature of the atrial mechanism. Orthodromic and antidromic supraventricular tachycardia are treated in the stable patient with either drugs that block the AV node (digoxin, verapamil or propranolol) or with drugs that alter conduction through the accessory pathway (procainamide quinidine, disopyramide or lidocaine). Chronic prophylactic therapy with either group of drugs may be required. Unstable patients with supraventricular tachycardia or with atrial fibrillation and a rapid ventricular response are treated with electrical cardioversion. Atrial fibrillation with a ventricular response which is not rapid can be treated with drugs that slow conduction through the accessory pathway. However, digoxin and verapamil are contraindicated in these patients as in a few patients these drugs can shorten the refractory period of the accessory pathway promoting enhanced conduction with the potential for deterioration to ventricular fibrillation.

In subjects who are resistant to anti-arrhythmic drugs or those experiencing intolerable side effects, open surgical division of the pathway or closed ablation of the pathway with a catheter utilising electrical energy (or radiofrequency) are alternative modes of treatment.

VENTRICULAR TACHYARRHYTHMIAS

Ventricular arrhythmias can be classified into three broad categories: 1) ventricular premature

[1] A congenital abnormality in which the tricuspid leaflets are displaced into the right ventricle.

[2] Decremental conduction refers to prolonged conduction time with increasing heart rate.

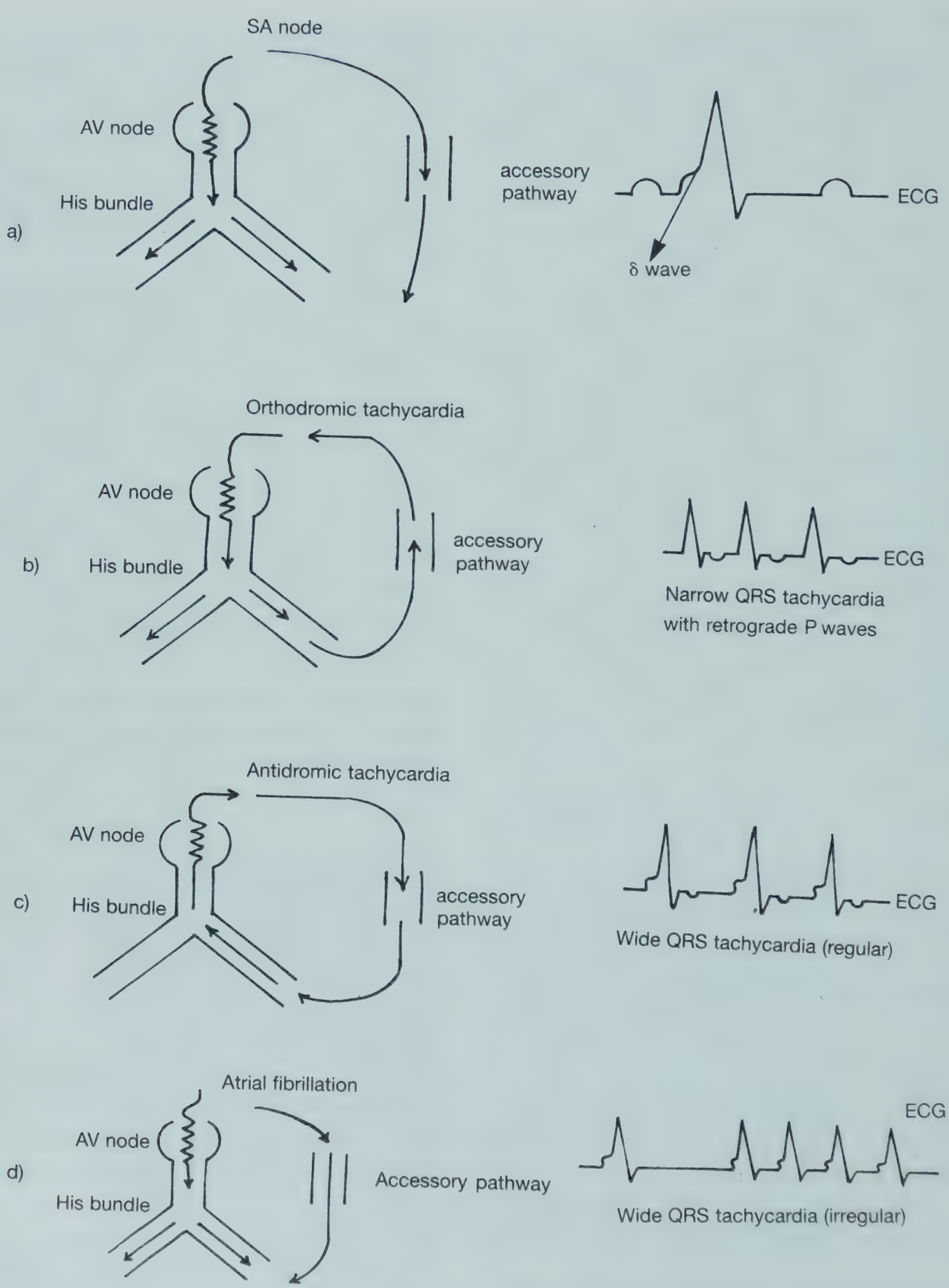


Fig 12.48 Schematic representation of the electrophysiology of WPW syndrome

beats, where one or two beats of ventricular origin precede the next sinus beat; 2) ventricular tachycardia, defined as three or more consecutive ventricular premature beats; and 3) ventricular fibrillation, defined as irregular, uncoordinated consecutive ventricular beats with an incoherent ECG tracing.

Ventricular premature beats

Ventricular premature beats are characterised by a wide QRS complex and are usually not preceded by a P wave (although retrograde ventriculoatrial activation may occur). There is usually a full compensatory pause. The terms *bigeminy* and *trigeminy* refer to arrhythmias where every second or third beat, respectively, is premature. Ventricular ectopic beats are quite common in normal persons and have been associated with caffeine intake, alcohol intake, stress and anxiety. No treatment is required unless structural heart disease is present. Even if heart disease is present, there is little evidence to suggest that the treatment of asymptomatic arrhythmias is beneficial. Antiarrhythmics should be used only if symptoms are present and intolerable.

Ventricular tachycardia (VT) (Fig 12.49)

The usual rate of ventricular tachycardia varies from 160–240 beats/minute. VT is moderately regular but less so than atrial tachycardia. VT may be *sustained* (lasting for more than 30 seconds) or *non-sustained* (<30 seconds). The causes of VT include coronary artery disease, cardiomyopathies, several forms of myocardial diseases, right ventricular dysplasia, alcoholism and the long QT syndrome. VT may occasionally be idiopathic. The ECG shows broad QRS tachycardia. One important differential diagnosis is supraventricular tachycardia with aberrant conduction. The ECG features favouring the possibility of VT are listed in Table 12.22. VT may be asymptomatic or associated with symptoms ranging from mild uneasiness to hemodynamic collapse.

Non-sustained recurrent VT need not be treated unless symptoms are present or a sustained VT is inducible. The treatment of sustained VT depends on how well the patient tolerates the arrhythmia. If the patient is hemodynamically unstable, immediate electrical cardioversion (synchronised DC shock of 200–360 joules) should be attempted. If the patient is stable, an intravenous bolus of lidocaine (1 mg/kg over 2 minutes) should be given with a further bolus of 0.5 mg/kg after 5 minutes in case no response is obtained with the first bolus. An infusion of 4 mg/min (2 mg/min in patients >65 years) should be started; if continued for more than 12 hours,

Table 12.22 ECG features suggesting ventricular tachycardia

Fusion beats		
Capture beats		
Atrioventricular dissociation (independent P wave activity)		
Left axis deviation		
QRS duration > 140 ms		
QRS morphology	Concordance (all complexes upright or inverted) in V_1-V_6	
	RBBB pattern	R wave in V_1 > R′
		Deep S wave in V_6
	LBBB pattern	R wave >30 ms duration
		Any Q wave in V_6
		>60 ms from onset of the QRS to nadir of the S wave in V_1 or V_2, notching of the downstroke of the S wave in V_1 or V_2

LBBB = left bundle branch block; RBBB = right bundle branch block

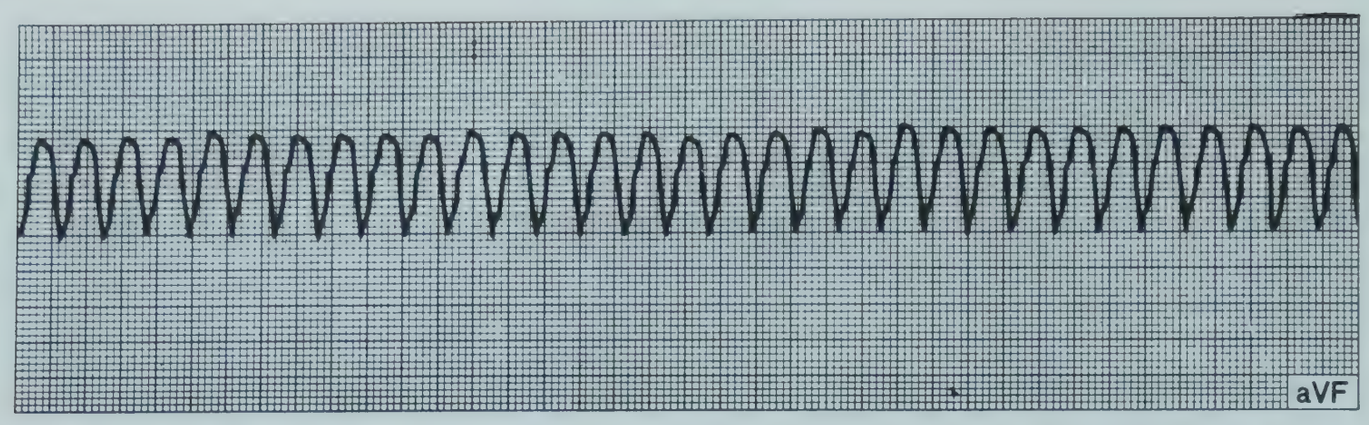


Fig 12.49 Ventricular tachycardia : rate variable from 140–250 beats per minute, slightly irregular rhythm, wide, slurred QRS complexes of ventricular premature beats, ST segment and T waves indistinguishable. There is an independent slower P rate but the P waves are often obscured.

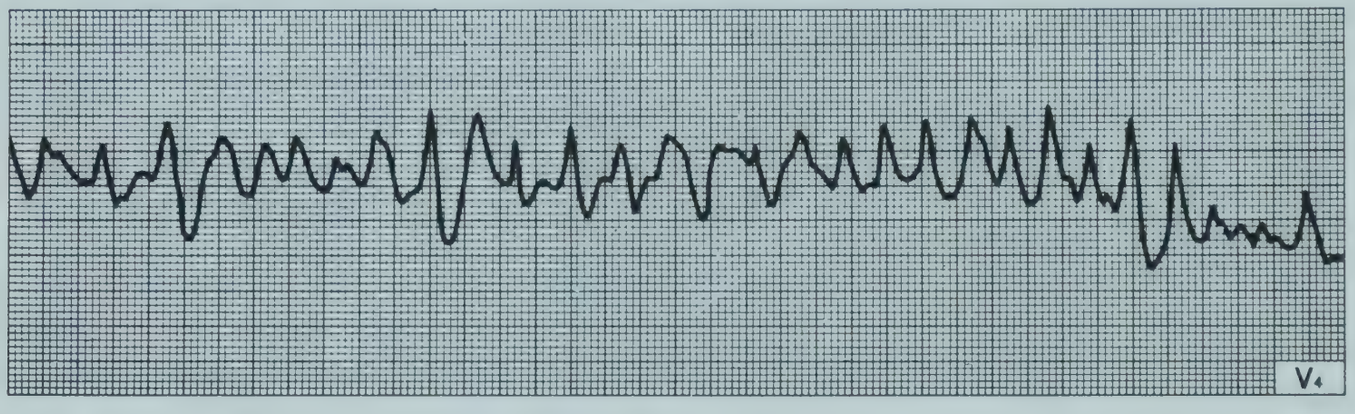


Fig 12.50 Ventricular fibrillation : rapid rate, irregular rhythm, no discrete complexes, may terminate in asystole as terminal event

toxicity may occur. If the second bolus is also ineffective and the patient is stable, intravenous procainamide (100 mg over 5 minutes, followed by 20–80 mg/kg/minute) can be tried; bretylium (5 mg/kg i.v. followed by an infusion of 1–2 mg/minute) may also be tried in cases of treatment failure. Patients with recurrent sustained VT merit a trial of pharmacologic arrhythmia suppression. Long term prophylaxis with Class Ia, Ib, Ic, II or III drugs can be attempted; there is some concern regarding the benefit-risk ratio for Class Ic agents. Patients who do respond to pharmacologic treatment are candidates for either the insertion of an automatic implantable cardiac defibrillator or for the ablation of arrhythmic foci using radiofrequency catheters.

Torsade des pointes

Torsade des pointes (TDP)[1] is a type of VT characterised by a specific ECG morphology that must be identified and differentiated from other types of VT due to important therapeutic differences. The ECG in TDP shows varying QRS morphology that changes in the direction of its vector, that is, twists about the baseline. The underlying abnormality is a prolongation of the QT interval; two important congenital syndromes are associated with prolongation of the QT interval: the *Jervell-Lange-Nielson* syndrome (autosomal recessive with deafness) and the *Romano-Ward syndrome* (autosomal dominant without deafness). Class I and III antiarrhythmic agents should be strictly avoided as they prolong the QT interval. Beta-blocking drugs are the agents of choice.

Ventricular fibrillation (VF) (Fig 12.50)

VF is a lethal arrhythmia unless reversed by DC cardioversion. Coronary disease is the leading cause of VF. It may occur in the absence of any myocardial damage ('out of hospital sudden death') or with acute myocardial infarction. Two types have been described after acute

[1] 'Twisting of points' in French

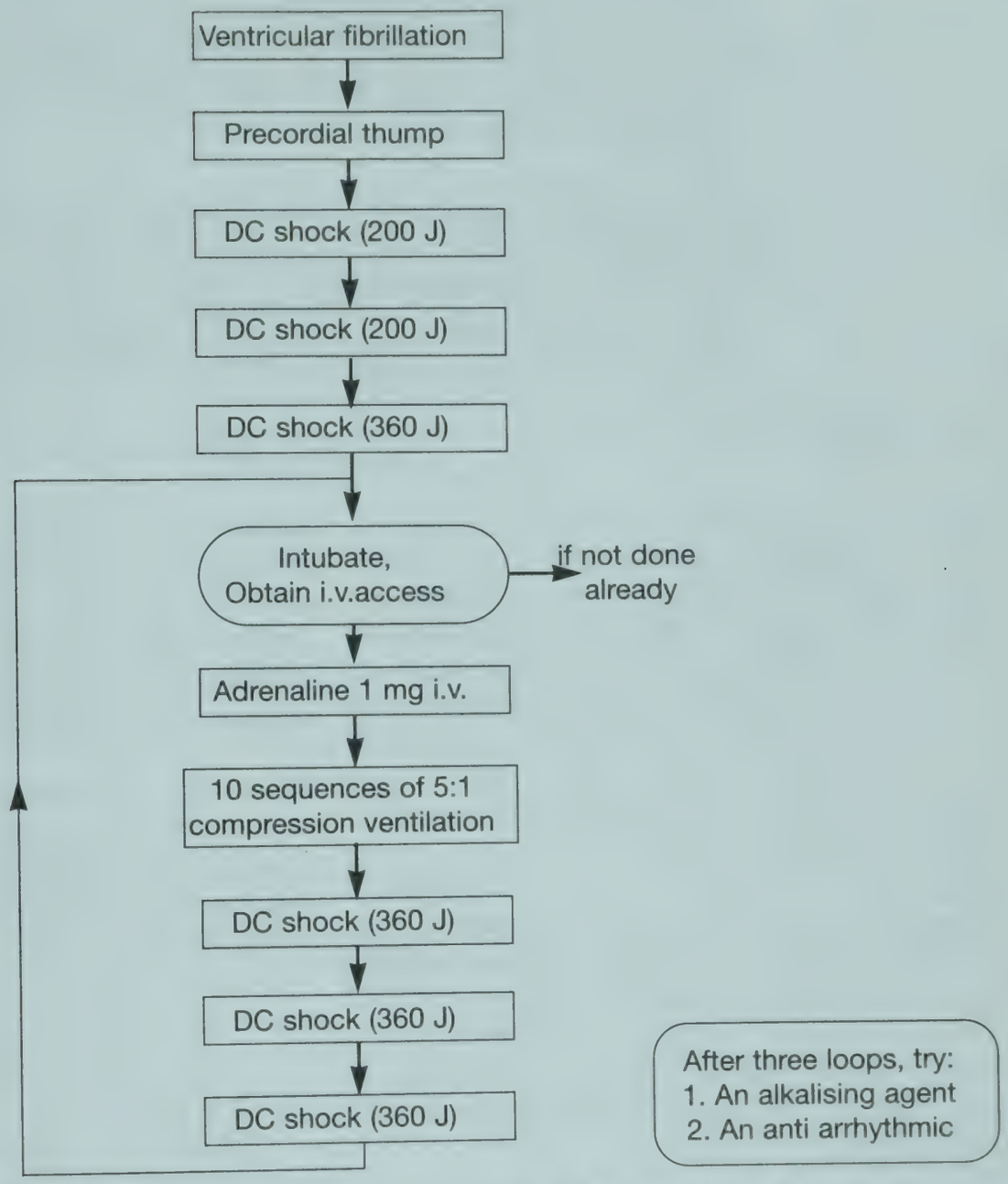


Fig 12.51 Algorithm for the management of cardiac arrest due to ventricular fibrillation

myocardial infarction. Primary VF usually occurs in the first few hours after myocardial infarction, responds well to cardioversion and is associated with an excellent prognosis. Secondary VF complicates myocardial infarction associated with severe myocardial damage; resuscitation is successful in less than 30 per cent and the arrhythmia indicates an adverse prognosis. Fig 12.51 outlines the treatment for VF. Subjects who survive 'out of hospital sudden death' need detailed investigation including exercise testing, coronary angiography and invasive electrophysiological studies.

DISTURBANCES OF IMPULSE GENERATION AND CONDUCTION (BRADYARRHYTHMIAS)

Sick Sinus Syndrome

ECG recognition (Fig 12.52) Sick sinus syndrome is a heterogeneous entity wherein there is evidence of sinus node dysfunction producing clinical symptoms. It refers to a spectrum of arrhythmias such as sinus bradycardia, sinus arrest, sinoatrial block, paroxysmal supraventricular tachycardia alternating with

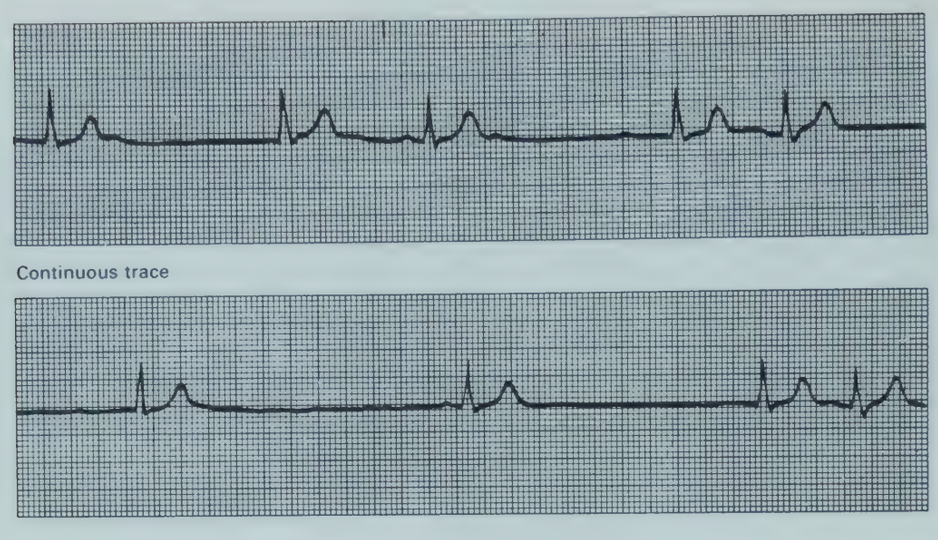


Fig 12.52 Sick sinus syndrome: note the long sinus pauses wherein the sinus node fails to fire, and the slow AV nodal 'escape' focus rate

periods of bradycardia or asystole (brady-tachy- syndrome), atrial fibrillation or flutter with a slow ventricular response, and failure to restore sinus rhythm following cardioversion. Sick sinus syndrome represents a generalised disorder of the conduction system of the heart, sinus node dysfunction being only one aspect. Varying degrees of AV nodal block and hemiblocks, and incomplete or complete bundle branch blocks may coexist.

Etiology The sick sinus syndrome may represent sclerodegenerative changes in the conduction system. It may also be the result of coronary disease, hypertension, residue of previous cardiac surgery or infiltrative myocardial disease (amyloidosis, hemochromatosis, sarcoidosis).

Clinical features Typically, men and women in the 60–65 years age group are equally affected. The presentation may be as syncope, presyncope (lightheadedness), palpitations or occasionally, as decreased exercise tolerance. There may be associated thromboembolic phenomena such as a stroke, due to development of atrial thrombi.

Electrophysiology A routine ECG or ambulatory ECG monitoring may reveal evidence of a sick sinus syndrome. Occasionally pharmacologic testing or invasive electrophysiologic testing is needed. The failure of the sinus rate to increase above 90 beats/minute with intravenous injection of a standard dose of atropine or isoproterenol may suggest the diagnosis. Delayed resumption of sinus node activity after a burst of rapid atrial pacing (prolonged '*sinus node recovery time*') may indicate a diseased sinus node.

Treatment Permanent pacing in a physiologic mode is the preferred treatment for patients who experience documented symptomatic brady-arrhythmias. Antiarrhythmic drugs may be required to treat symptomatic tachy-arrhythmias.

Carotid Sinus Hypersensitivity (CSH)

This is a condition of enhanced responsiveness to carotid sinus stimulation manifesting either as prolonged ventricular asystole exceeding 3 seconds (*cardioinhibitory type*) or as a decrease in systolic blood pressure exceeding 50 mmHg (*vasodepressor type*). The stimulus may be tight neck collars or physician testing.

Treatment Avoidance of tight collars, rapid neck movements and drugs which enhance CSH (like digitalis, clonidine, alphamethyldopa, propranolol) are essential. Severe symptoms with a cardioinhibitory type of response can be treated with a permanent ventricular pacemaker. The vasodepressor type is difficult to treat requiring mineralocorticoid supplements or even surgical denervation of the carotid sinus.

Unifascicular Block

Left anterior hemiblock (LAH)

Blockage of the left anterior division of the left bundle (left anterior hemiblock) causes a distinctive electrocardiographic abnormality characterised by marked left axis deviation. The cardiac impulse enters the left ventricle by way of the left posterior division; consequently, the initial QRS forces are directed inferiorly and posteriorly. The electrocardiographic features of left anterior hemiblock are:

1. The frontal plane QRS axis is negative, at least −45° and the QRS duration is normal. No other cause for marked left axis deviation is present (such as pulmonary emphysema, kyphoscoliosis or congenital heart disease).
2. A small R wave followed by a large S wave is present in leads II, III, and aV_F, and small Q waves are seen in leads I and aV_L.

The natural history of isolated left anterior hemiblock is benign.

Left posterior hemiblock (LPH)

Blockage of the left posterior fascicle is less common compared to block of the anterior facicle because of its better vascular supply. The electrocardiographic features of LPH are:

1. There is right axis deviation generally greater than +110° in the absence of any other cause for right axis deviation (right ventricular hypertrophy, emphysema, or pectus excavatum).
2. rS complexes are seen in leads I and aV_L and a very small Q wave is followed by a large R wave in leads II, III, and aV_F.

Bifascicular Block

Slowing of conduction in two of the three fascicles of the infrahisian conduction system represents a bifascicular block. Thus, a pattern of right bundle branch block with left anterior hemiblock, or left bundle branch block itself, or right bundle branch block with left posterior hemiblock are examples of bifascicular block. RBBB with LAH is manifested electrocardiographically as right bundle branch block and marked left axis deviation; causes of this pattern include congenital defects in the area of the AV canal, degenerative disease, and a variant pattern (observed in 1 per cent of normal adults). When a bifascicular block is present, the development of block in the remaining normal fascicle will result in complete heart block; the incidence of progression to complete heart block over five years in chronic bifascicular block is less than 1 per cent per year. Survival in these subjects is related more to other clinical indicators such as advanced age, associated coronary artery disease or congestive heart failure. Therefore, insertion of pacemakers is recommended in patients with chronic bifascicular blocks only if symptomatic bradyarrhythmias can be documented.

Pacing is also recommended in subjects with a bifascicular block that persists after acute anterior myocardial infarction, if the patient has experienced transient complete heart block during the acute phase of infarction.

Atrioventricular Block

Atrioventricular block represents conduction disturbance in the AV node or the His bundle proximal to the fascicles. Three types are recognised electrocardiographically.

First degree AV block (Fig 12.53)

First degree AV block is defined as a PR interval greater than 0.20 second (at a heart rate of 70).[1] In the absence of a bundle branch block, prolongation of the PR interval is usually caused by a delay at the level of the AV node. When bundle branch block is present, conduction may be delayed either at the AV node or distal to it; His bundle electrocardiography is then required to localise the exact site of the block. Causes of a prolonged PR interval include age-related degenerative changes in the AV conduction system, drugs (such as digitalis), increased vagal tone, ischemia affecting the AV node (as in inferior wall myocardial infarction), inflammation of the heart (such as myocarditis or acute

[1] The upper limit of the normal PR interval decreases progressively as the heart rate increases, being 0.17 second at a rate of 115 beats/minute

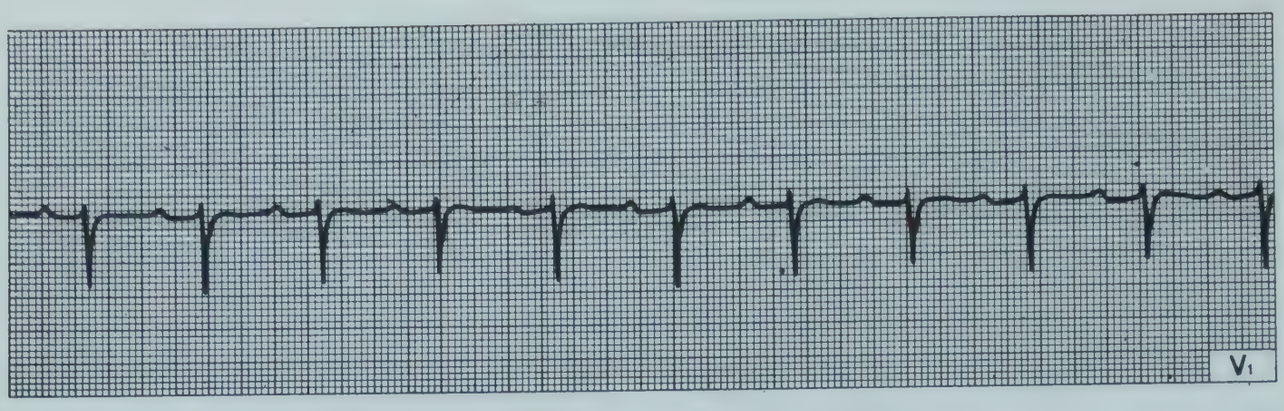


Fig 12.53 Incomplete AV block (first degree): PR interval >0.2 second, prolonged AV conduction time only, ventricular rhythm regular without dropped beats

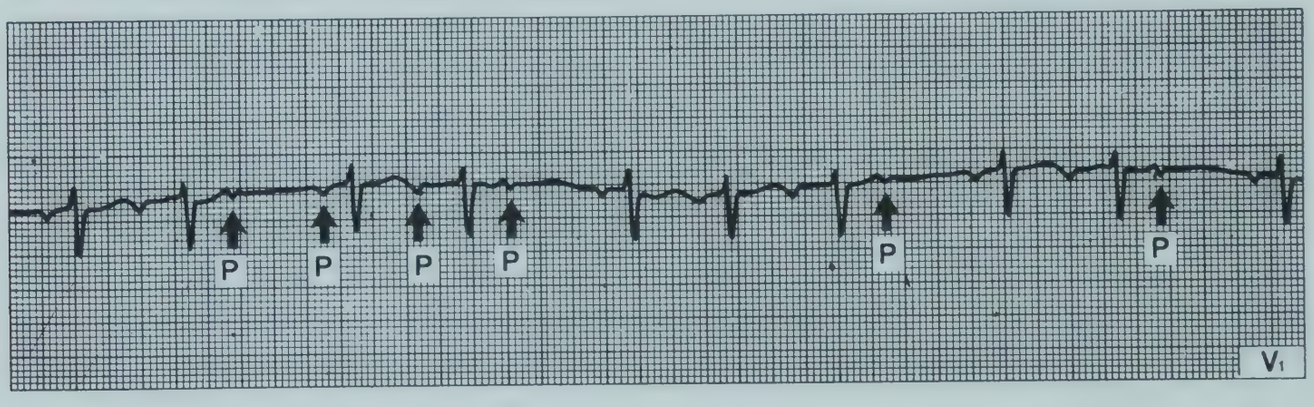


Fig 12.54 Incomplete AV block (Wenckebach phenomenon): cyclic progressive lengthening of PR interval in successive beats until a beat is dropped; arrows = P wave (Mobitz type I)

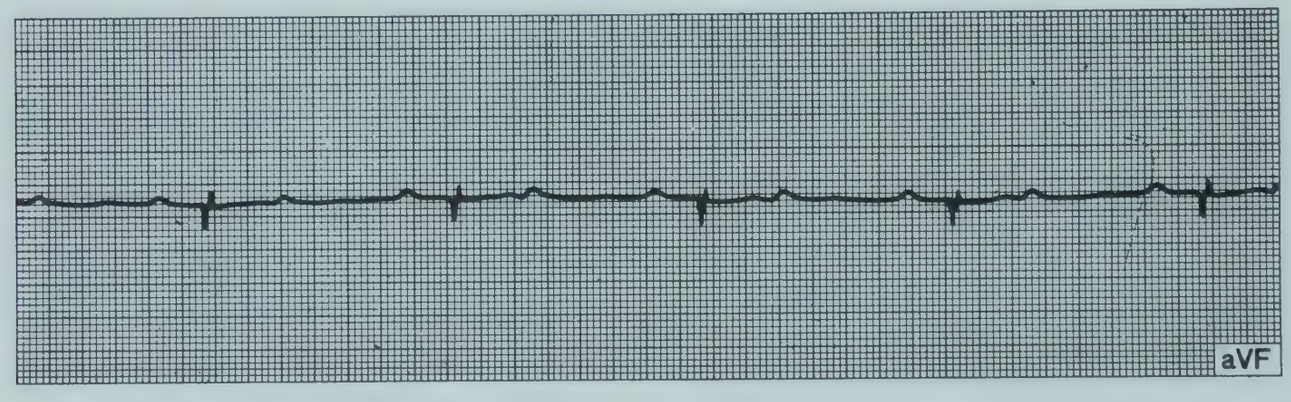


Fig 12.55 Incomplete AV block (second degree, Mobitz II): 2:1 block with alternate response of ventricle to atrial beats, regular P-P intervals. When any but not all ventricular beats are dropped, second degree AV block exist

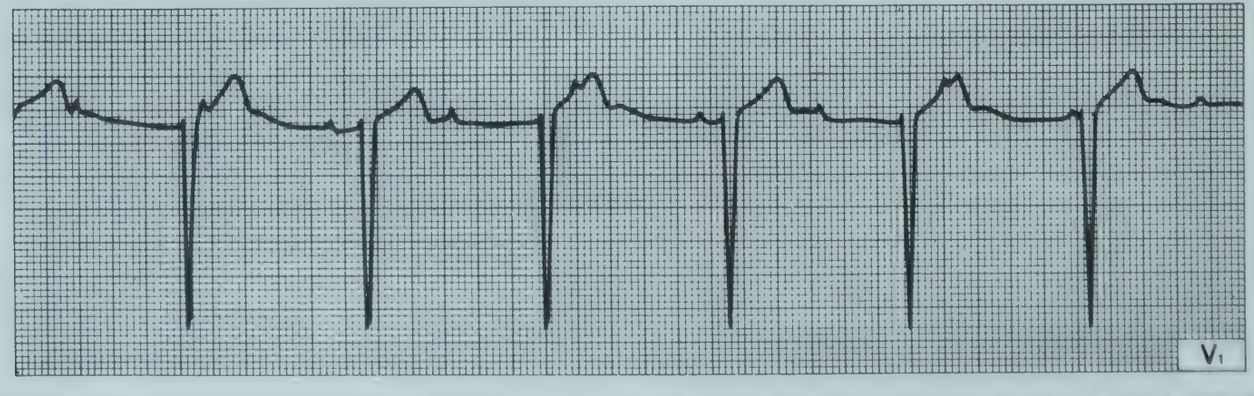


Fig 12.56 Complete AV block (third degree): independent regular atrial and ventricular rhythms, atrial rate 72 per minute, ventricular rate 54/minute, SA impulses do not depolarise the ventricles

rheumatic fever), valvular heart disease (severe aortic regurgitation) and cardiomyopathies (primary and secondary). Clinical examination is unremarkable except for the presence of a soft first heart sound. First degree AV block has a benign clinical course.

Second degree AV block (Figs 12.54, 12.55)

There are two types of second degree AV block: Type I (also called Wenckebach or Mobitz I) block is usually caused by AV nodal conduction delay, whereas Type II (Mobitz II) block is the result of infranodal block; Type II block has a worse prognosis because of frequent progression to complete heart block. In Type I, there is a progressive prolongation of the PR interval until a beat is finally blocked. Once a dropped beat occurs, the sequence is repeated. In contrast, Type II is manifested as a sudden interruption of AV conduction without prior prolongation of the PR interval. Type I sometimes responds to atropine, 0.5 to 1.5 mg intravenously; such therapy is reserved for the reversal of transient excessive vagal tone in a medical emergency such as acute myocardial infarction. Symptomatic second degree heart block requires electrical pacing.

Third degree (complete) AV block (Fig 12.56)

In a third degree AV block, all atrial beats are blocked and an ectopic escape focus distal to the block drives the ventricles. When the block is AV nodal, the escape rhythm arises in the AV junction, has a rate of 44–55 beats/minute and the QRS is of a normal duration. When the AV block is infranodal, the escape focus is in the common bundle or the ventricles, the escape rate is slow (30–45 beats/minute) and the QRS complex is wide; the slower escape rate and higher incidence of asystole render this more hazardous than nodal blocks. The causes of complete heart block include congenital heart block, degenerative age-related changes in the conduction system (*Lenegre's disease*), coronary artery disease, and infectious or inflammatory processes (myocarditis, rheumatic fever, Lyme disease, ankylosing spondylitis, myocardial abscesses, myocardial tubercles, tumours, infiltrative diseases of the myocardium, sarcoid nodules and gummas). Congenital complete heart block presents in infancy and is associated with the presence of maternal antibody to the soluble ribonucleoprotein antigen Ro (or SS-A). *Adams-Stokes attacks* and congestive heart failure are the principal manifestations of a complete heart block. Adams-Stokes attacks are syncopal episodes caused by either sudden asystole or the development of ventricular tachyarrhythmias that lead to circulatory arrest. Adams-Stokes attacks are sudden in onset. Patients recover consciousness rapidly and are immediately awake and oriented if adequate cerebral perfusion is restored promptly. The bradycardia associated with complete heart block may occasionally lead to congestive heart failure in patients with underlying myocardial disease. The clinical signs of a complete heart block include bradycardia, and signs of AV dissociation (variations in systolic blood pressure, intensity of the first heart sound, intermittent cannon waves in the jugular venous pulses and variable third and fourth heart sounds).

Electrical pacing is the treatment of choice for symptomatic complete heart block. In patients with complete heart block who have a very slow ventricular rate, intravenous isoproterenol (1 to 4 mg/min) can be given until pacing can be established.

Indications for pacemaker insertion in AV blocks

The indications for permanent pacing in AV blocks are:

1. second or third degree AV block associated with symptoms of syncope provided symptomatic bradycardia has been documented;
2. complete heart block with congestive heart failure, with or without syncope;
3. complete heart block that persists after acute anterior myocardial infarction even if it is asymptomatic.

Table 12.23 Classification of antiarrhythmic drugs

Class/Prototype Agent	*Dosage*		*Side effects*	*Main indications*
	Oral	*Intravenous*		
Class I : Sodium channel blockers				
Ia. Slow rate of rise of action potential, prolong its duration, slow conduction and increase refractoriness				
Quinidine	200–400 mg q 4–6 hr	6–10 mg/kg i.m.or i.v. over 20 mins	gastric, increases digoxin levels, syncope	• supraventricular tachycardia
Procainamide	50 mg/kg/d in 4–6 divided doses	100 mg over 1–3 mins; maintain infusion at 2–6 mg/min	SLE, hypersensitivity, negative inotropic effect	• ventricular tachycardia • prevention of ventricular fibrillation
Disopyramide	100–200 mg q 6-8 hrs	–	urinary retention, dry mouth, negative inotropic effect	
Ib. Shorten action potential duration, do not affect conduction or refractoriness				
Lidocaine	–	1–2 mg/kg bolus at 50 mg/min; maintain at 1–4 mg/min	convulsions, gastric hypotension	• Ventricular tachycardia • symptomatic ventricular extra beats • arrhythmia due to digitalis toxicity (phenytoin)
Tocainide	200–400 mg q 6–8 hr	–	leukopenia, gastric, CNS	
Mexilitene	100–300 mg q 6–12 hr; maximum 1200 mg/24 hr	–	CNS, gastric, leukopenia	
Phenytoin	200–400 mg every 12–24 hr	12 mg/kg bolus at 50 mg/5 mins; maintain 200–400 mg/d	CNS, gastric	

Table 12.23 Classification of antiarrhythmic drugs (contd.)

Class/Prototype Agent	Dosage		Side effects	Main indications
	Oral	*Intravenous*		
IC. Slow rate of rise of action potential, slow repolarisation more than Class Ia. Propafenone is a weak calcium channel- and beta-blocker				
Flecainide	100–200 mg bid		negative inotrope, CNS, incessant VT	• life-threatening VT or VF • resistant supraventricular tachycardia
Propafenone	150–300 mg q 8 hrs		negative inotrope, increases digoxin levels, CNS	
Class II : Beta-blockers : slow AV conduction				
Propranolol	40–320 mg/d in divided doses	1–5 mg at 1 mg/min	bradycardia, bronchospasm, negative inotrope	• supraventricular tachycardia • prevention of ventricular fibrillation
Esmolol		500 μg/kg over 1–2 min; maintain at 25–200 μg/kg/min	negative inotrope, bronchospasm	
Class III agents : Block potassium channels, prolong repolarisation, widen QRS and QT; Sotalol has beta-blocking effect				
Amiodarone	800–1600 mg/day for 3 weeks; maintain at 100–400 mg/day		Pulmonary fibrosis, hypo-, hyperthyroidism, corneal and skin deposits, hepatitis, neuropathy	• refractory ventricular tachycardia • supraventricular tachycardia • prevention of VT/VF
Sotalol	80–160 mg q 12 hr		negative inotrope, other side effects of beta-blockers	• ventricular tachycardia
Bretylium		5–10 mg/kg; maintain at 0.5–2 mg/min	hypotension, gastric	• ventricular fibrillation, • ventricular tachycardia

Table 12.23 Classification of antiarrhythmic drugs (contd.)

Class/Prototype Agent	*Dosage*		*Side effects*	*Main indications*
	Oral	*Intravenous*		
Class IV : Calcium channel antagonists: decrease automaticity and slow AV conduction				
Diltiazem	180–360 mg/day in 3 doses	0.25 mg/kg over 2 mins; repeat after 15 mins if no response; maintain 5–15 mg/hr	negative inotrope, hypotension	supraventricular tachycardia
Verapamil	80–120 mg q 6–8 hr; sustained release 240–360 mg/d	10–20 mg over 5 mins; maintain at 5 µg/kg/min	constipation, increases digoxin levels	
Class V				
Adenosine	–	6 mg rapidly followed by 12 mg after 2 mins if required	chest pain, flushing, sinus bradycardia, AV block	supraventricular tachycardia
Digoxin	1–1.5 mg in 3–4 doses over 24–36 hrs; maintain 0.125–0.25 mg/day	0.5 mg over 20 mins followed by increments of 0.25 or 0.125 mg every 6 hrs to a maximum of 1.5 mg/24 hr	gastric, CNS, visual halos	

CARDIAC ARREST AND CARDIOPULMONARY RESUSCITATION

Cardiac arrest is the sudden complete loss of cardiac function. Either the heart or the respiration may fail first, the two events being closely related. The immediate causes of cardiac arrest are arrhythmias, ventricular fibrillation, asystole or electromechanical dissociation. The clinical diagnosis of cardiac arrest is made when the patient has collapsed and is pulseless, is not breathing and no heart sounds can be

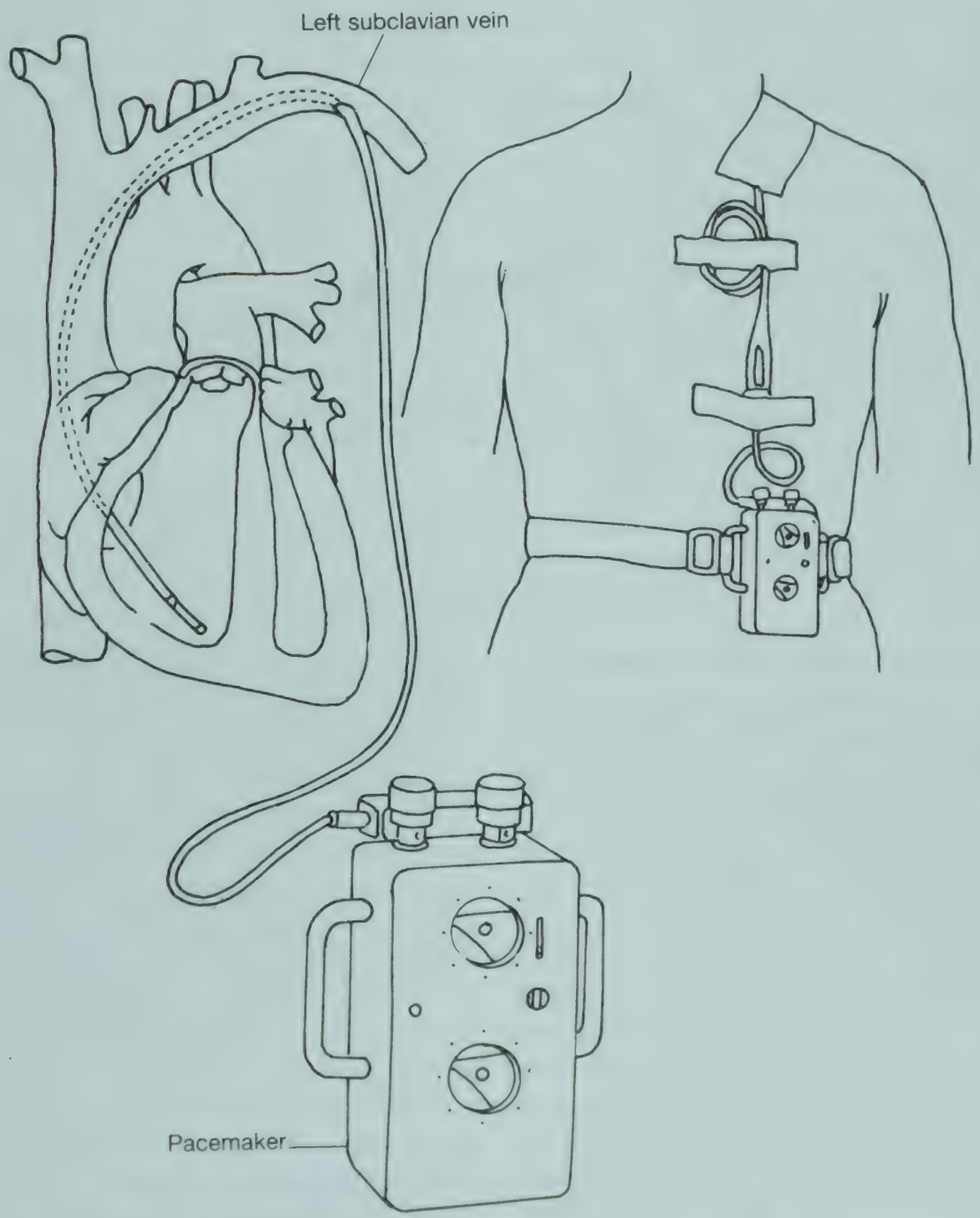


Fig 12.57 Temporary pacemaker: the transvenous catheter electrode is attached to a battery-powered external pacemaker. The catheter is wedged in the apex of the right ventricle.

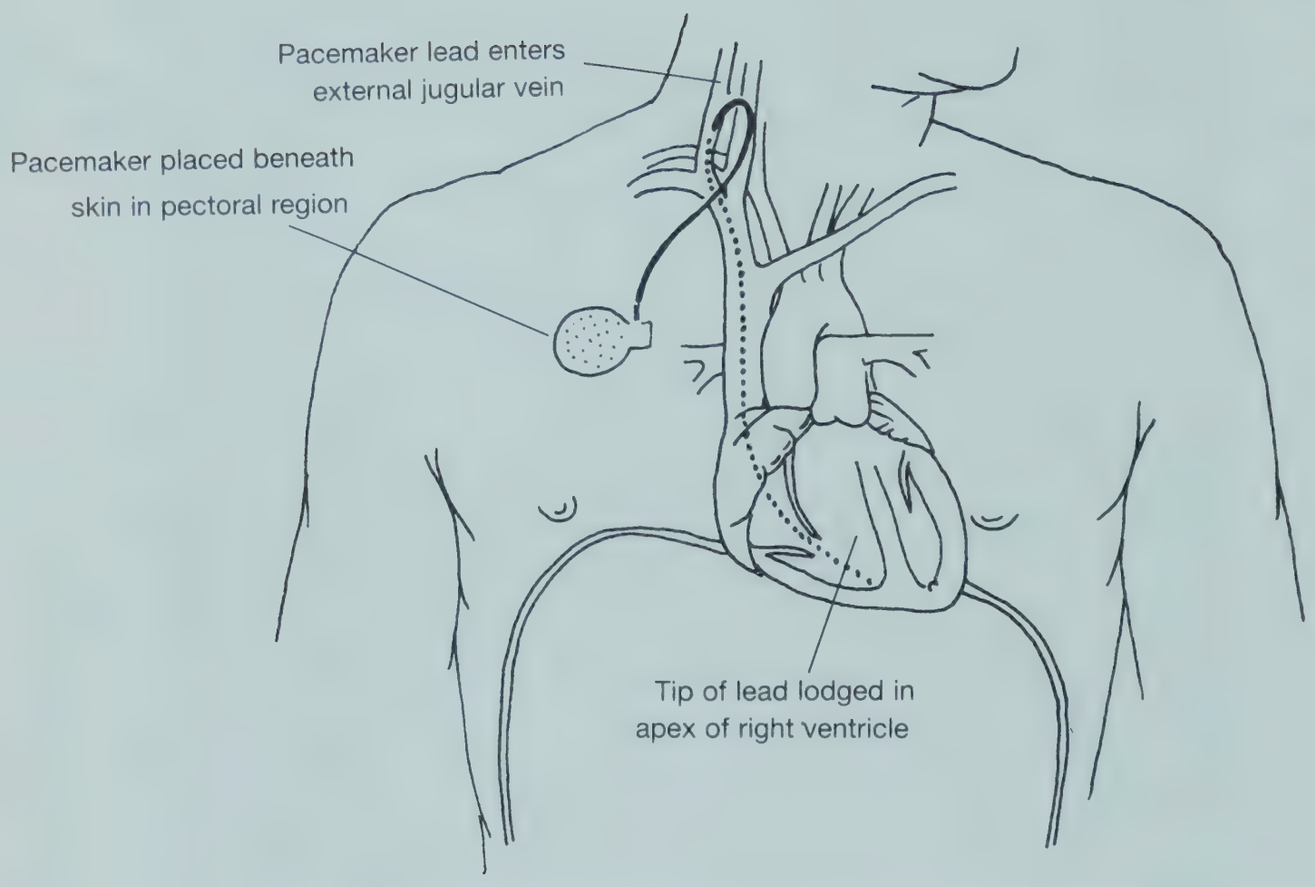


Fig 12.58 Permanent pacemaker

auscultated. Cardiopulmonary resuscitation (CPR) must be instituted immediately. CPR consists of basic life support (BCLS) followed by advanced cardiac life support (ACLS). Basic life suuport consists of the 'ABCs'. The airways (A) should be cleaned and the tongue removed from the posterior pharynx by tilting the head back and hyperextending the neck, provided cervical spine injury is not a possibility. If no breathing is noted, artificial respiration should be initiated with 'mouth to mouth' breathing (B) and continued until a facemask or bag become available. If a carotid pulse is not present, external cardiac compression (C) should be commenced. The lower half of the sternum should be depressed 3 to 5 cm, at a rate of about 80 times per minute with the patient lying on a hard surface. A single rescuer must give twenty chest compressions alternating with two ventilations every 15 seconds. If two rescuers are present, a ratio of five chest compressions per ventilation may be used.

ACLS consists of obtaining an ECG to determine the cardiac rhythm, restoring intravenous access, instituting appropriate drug or electrical treatment for the underlying arrhythmia, providing respiratory support and maintaining circulation. The management of VF has already been outlined in Fig 12.51; defibrillation should be applied promptly. For asystole, intravenous atropine (0.6–1.2 mg) can be administered followed by intravenous adrenaline (1 mg, i.e. 10 ml of a 1:10,000 solution) if there is no response to atropine. If an intravenous line is available, the drugs can be administered through an endotracheal tube if one has been secured. Temporary cardiac pacing must be considered, with an external pacemaker

if available. Because of potential complications such as pneumothorax, coronary vessel laceration and tamponade, intracardiac adrenaline is not recommended unless intravenous or airway routes are unavailable. Electromechanical dissociation (EMD) refers to the presence of electrical cardiac activity in the absence of mechanical activity. It may be caused by an underfilled ventricle (tamponade) or severe myocardial depression. If cardiac tamponade is suspected, immediate pericardiocentesis should be attempted. A tension pneumothorax is another cause of EMD that can be remedied by immediate needle placement or chest tube insertion.

Pharmacologic treatment of cardiac arrhythmias

The major classes of antiarrhythmic drugs, their doses and indications are summarised in Table 12.23.

Pacing techniques

Temporary pacemakers, which are required for the management of symptomatic bradycardia in many different circumstances, can be inserted from the jugular, subclavian or femoral veins (Fig 12.57). An effective external pacing device suitable for use in emergencies has also been developed. Permanent pacemakers are inserted for the management of symptomatic bradyarrhythmias, complete heart block or symptomatic high grade AV blocks. Permanent pacemakers consist of an electrode inserted either through a cephalic or external jugular vein into the apex of the right ventricle and attached to a subcutaneous power source buried just inferior to the clavicle (Fig 12.58). A second electrode is inserted through the same or a nearby site into the right atrium for dual chamber pacing. Rapid advances in electrode design, pacemaker circuitry, and the introduction of new power sources (lithium batteries) have reduced the size and prolonged the life of pacemaker pulse generators. The availability of complex and multiprogrammable dual chamber pacemakers has also led to the development of a uniform terminology for the description of pacemakers. The Inter-Society Commission on Heart Disease (ICHD) five-position pacemaker code classification scheme has achieved widespread acceptance. This code assigns one position to each of the five major characteristics of an implantable pacemaker as follows: the chamber(s) paced (position 1), the chamber(s) sensed (position 2), the mode of response(s) to sensed event (position 3), programmable functions (position 4), and special tachyarrhythmia functions (position 5). In practice, only the first three positions describe the commonly used pacemakers. For example, a pacemaker that paces the ventricle, senses the atrium and is triggered by a sensed atrial event would be classified as a VAT pacemaker. A standard ventricular demand (inhibited) pacemaker is classified as a VVI pacemaker. Pacemakers should be chosen wisely and tailored to the activity and anticipated lifespan of the recipients. Most pulse generators and lead systems have an early failure rate below 5 per cent and a life expectancy ranging from 4 to 10 years.

Electrical Treatment of Cardiac Arrhythmias

Defibrillation and cardioversion

Electrical energy is often used for terminating cardiac tachyarrhythmias. The term *defibrillation* is used when an *unsynchronised* electrical discharge is applied to the heart during ventricular fibrillation (VF). The resultant cardiac asystole is terminated by the emergence of the rhythm of the dominant cardiac pacemaker, usually the sinoatrial node. *Cardioversion* is the use of *synchronised* electrical discharge to revert cardiac tachyarrhythmias other than VF. In VF, when the entire heart muscle is fibrillating, synchronisation of the electrical discharge is not required. For all other tachyarrhythmias the electrical discharge is synchronised with the R wave of the surface ECG to avoid delivering a discharge during the 'vulnerable period' of the

ventricle. The 'vulnerable period' refers to a time span of 30 milliseconds just before inscription of the apex of the T wave of the surface ECG. An impulse delivered during this period can trigger VF, that is, the ventricle is vulnerable to fibrillation at this time.

Principle The physiologic basis for the use of electrical energy is that the electrical discharge depolarises a part of the 'reentry path' rendering it refractory, thus interrupting the circus movement which underlies the basis of most tachyarrhythmias.

Method Both cardioversion and defibrillation make use of a source of electrical energy called the defibrillator. The defibrillator has two paddles and a circuitry for synchronising the discharge with the R wave of the surface ECG lead it monitors. A switch on the machine helps to select a synchronised or an unsynchronised mode of energy delivery. When a synchronised mode is selected, the trigger can be positioned on the R wave of the monitored ECG either manually (synchronisation artifact on the screen display) or automatically. Another switch helps select the level of energy delivered which may depend on the type of underlying tachyarrhythmia (Table 12.24).

The *paddles* are the electrodes used for transmitting the electrical energy and are usually marked as 'STERNUM' and 'APEX' to indicate the relative position of the paddles. The electrical energy is delivered to all body structures between the two electrodes. The paddles are covered completely with a conductive gel, especially around the edges to reduce the likelihood of skin burns. The 'sternal' paddle is held *firmly* along the right sternal border at the level of the second and third intercostal spaces. The 'apex' paddle can be placed either between the apex and anterior axillary line (anterolateral paddle position) or at the angle of the left scapula (anteroposterior paddle position). After selecting the requisite energy level and the synchronised or unsynchronised mode, the operator must press the charge button on one of the paddles whereupon a whining noise coincides with a screen display of the level of energy selected. Finally the discharge button on both paddles is pressed to deliver the electrical energy. The operator must not touch the metal bed of the patient (this applies to all observing or assisting personnel). Since the procedure is associated with patient discomfort, unless performed as an emergency procedure for a hemodynamically unstable rhythm, all elective procedures must be preceded by sedation of the patient with small amounts of intravenous diazepam (5–15 mg). For elective procedures, it is desirable to obtain serum electrolyte levels and prothrombin time (if the patient is on oral anticoagulants) prior to the procedure. Equipment for cardiopulmonary resuscitation must be readily available. Blood pressure and respiration should be carefully monitored and a patent i.v. line available.

Table 12.24 Usual energy level required for cardioversion/defibrillation

Arrhythmia	*Energy required (watt seconds/joules)*
Ventricular tachycardia	100
Atrial flutter	20
Atrial fibrillation	100
Supraventricular tachycardia	25–50
Ventricular fibrillation	200–300

* Initial discharge is usually at the lowest energy required for a specific arrhythmia.

Risks The main danger of this transthoracic energy delivery is provocation of VF (unsynchronised impulse or improper synchronisation) and prolonged asystole (unmasking of a latent sick sinus syndrome). Other arrhythmias may occur because of the release of catecholamines, acetylcholine and

potassium. The risk is more in subjects with baseline dyselectrolytemia, digitalis intoxication or hyperthyroidism.

Muscle soreness is a common complaint after the procedure and may be accompanied by a concomitant rise in serum levels of LDH, creatine kinase (CK). Elevation of CK MB isoenzyme generally does not usually occur until the total energy delivered to the patient exceeds 425 watt seconds.

Success rate Successful reversion to sinus rhythm occurs in 90 per cent of patients with reentrant supraventricular tachycardias, ventricular tachycardia and fibrillation, and recent onset atrial flutter and fibrillation.

KEY CONCEPTS

- Bradyarrhythmias arise from abnormalities of the intrinsic automatic pacemakers or due to abnormalities within the AV node or the His-Purkinje system.
- Tachyarrhythmias arise by one of 3 possible mechanisms: reentry (majority), increased automaticity, or triggered activity.
- 24-hour ambulatory ECG monitoring is a powerful method of capturing arrhythmic events when they are frequent and also serves to document the correlation of symptoms with the electrical events.
- Invasive electrophysiologic studies are indicated when spontaneous arrhythmias are infrequent and a serious sustained arrhythmia is suspected. Programmed electrical stimulation is used to initiate and terminate reentrant arrhythmias and to assess the response of the induced arrhythmia to antiarrhythmic drugs.
- Most antiarrhythmic agents belong to one of 4 categories:
  - (i) Class I drugs are sodium channel (rapid inward current) blockers; all reduce the rate of depolarisation of the action potential and slow conduction; Class Ia (quinidine, procainamide, disopyramide) prolong repolarisation, Ib (mexilitene, lidocaine, tocainide) accelerate repolarisation, while Ic (flecainide, encainide) have no effect on repolarisation.
  - (ii) Class II (beta-blocker) agents accelerate repolarisation and inhibit sympathetic tone.
  - (iii) Class III agents (amiodarone, sotalol) interfere with the potassium channel (plateau phase of action potential) and increase refractoriness.
  - (iv) Class IV drugs (calcium channel blockers) slow conduction and inhibit the slow inward calcium current.
  - (v) Digoxin shortens the atrial and the ventricular refractory periods but prolongs AV node conduction. Adenosine blocks or slows AV nodal conduction.

Paroxysmal supraventricular tachycardia

- PSVT is a narrow QRS tachycardia that may be due to AV nodal reentry, may involve an accessory pathway or may represent a true atrial automatic tachyarrhythmia.
- The most common mechanism involves AV nodal reentry; there is an intra- or paranodal fast pathway. There is antegrade conduction over the AV node (slow path) with retrograde conduction over the fast pathway. A majority of patients do not have any structural heart disease.
- Clinically, PSVT presents as an abrupt onset of palpitations with a heart rate varying between 160–200 beats/min. The P waves in the ECG are usually buried within the QRS complex.
- The treatment modalities include vagal stimulation (carotid sinus massage, Valsalva maneuver), i.v. adenosine or verapamil; DC cardioversion may be required if there is evidence of hemodynamic instability. Chronic prophylaxis may be instituted with verapamil, beta-blockers, or digoxin. Controlled radiofrequency ablation is an alternative which may be curative without causing any AV block.

Atrial fibrillation

- AF represents disorganised atrial depolarisation that results from chaotic wavelets of reentry.
- AF may occur in the absence of any structural heart disease (lone AF), or may be associated with valvular heart disease, coronary disease, systemic hypertension, cardiomyopathies and thyrotoxicosis. It may be chronic or paroxysmal.
- Symptoms include palpitations and fatigue. AF may precipitate angina, CHF or hypotension and is associated with an increased risk of systemic embolism.

- The ECG shows an irregularly irregular QRS rhythm with a rate of >350 beats/min; P waves may be absent or coarse fibrillary waves may be present.
- Treatment involves control of the ventricular response rate (usually by administering digoxin to increase AV nodal delay; beta-blockers and calcium channel blockers are adjuncts; digoxin is contraindicated if there is an underlying WPW syndrome), restoration of sinus rhythm (pharmacologically with Ia/Ic agents or amiodarone; DC cardioversion may be effective and sinus rhythm maintained if AF duration is short and LA is not enlarged), and prevention of systemic embolism with anticoagulation (oral anticoagulation to maintain an INR of 2-3) or antiplatelet drugs (aspirin, especially if oral anticoagulants are contraindicated).

Wolff-Parkinson-White Syndrome

- In the WPW syndrome there is an accessory pathway which links the atria and the ventricles and bypasses the AV node. The ECG features include a short PR interval and a slurred QRS complex (initial δ wave). Most patients have a structurally normal heart; an association has been described with Ebstein's anomaly of the tricuspid valve.
- The accessory pathway can initiate a reciprocating tachycardia. The tachycardia is most often orthodromic: activation from the atria to the ventricles occurs over the AV node while the return of the impulse occurs via the accessory path; this results in a narrow QRS tachycardia. An antedromic reciprocating tachycardia results in broad QRS tachycardia.
- No treatment is required where there is no history of tachycardia. Any narrow QRS tachycardia should be treated along the lines of a PSVT (with the caveat that digoxin and verapamil be avoided if there is atrial fibrillation). When there is AF, Class Ia/Ic agents or amiodarone are preferred. If the patient is hemodynamically unstable, electrical cardioversion is the treatment of choice. Surgical ablation should be considered when there is frequent symptomatic tachycardia with poor control on medication.

Ventricular tachycardia

- VT refers to greater than 3 consecutive ventricular beats at a rate of ≥120 beats/min; it may be monomorphic or polymorphic, sustained (≥30 seconds) or unsustained.
- Causes of VT include coronary artery disease (often during the acute phase of MI, or post-MI especially if accompanied by LV dysfunction and a dyskinetic LV segment), cardiomyopathy, antiarrhythmic agents, and CHF.
- A broad QRS tachycardia is likely to be VT if there is AV dissociation (independent P wave activity), fusion or capture beats, concordance of QRS vector in precordial leads, negative QRS frontal plane axis, and if the QRS duration is >140 milliseconds.
- If the patient is hemodynamically unstable, electrical cardioversion must be performed promptly. Medical measures in the stable patient include the following choices: i.v. lidocaine (or mexilitene), bretylium or procainamide. Long-term prophylaxis may be considered with Class I, II, or III agents. If a reentrant substrate is identifiable with electrophysiologic studies, surgical ablation should be considered.

Heart block

- Heart block is a disturbance of impulse conduction between the SA node and atria (SA block), between the atria and the ventricles (AV block) or within the ventricle (intraventricular and bundle branch blocks).
- Three types of atrioventricular blocks are recognised:
  - (i) First degree heart block occurs in young individuals, with digitalis use, and is associated with a benign prognosis. The PR interval is prolonged but there are no blocked impulses (S_1 is soft).
  - (ii) Second degree heart block may be of two types. In Mobitz I block (Wenckebach) the PP interval is constant but there is progressive prolongation of the PR interval leading to a dropped beat; the disturbance lies within the AV node. In Mobitz type II block, the QRS complexes are dropped every 2,3 or 4 beats but the PR interval is constant; this is a more serious arrhythmia and indicates an infranodal disturbance.
  - (iii) In third degree heart block the atria and the ventricles are under the control of separate pacemakers; the ventricular rate is maintained by a pacemaker below the AV node (except for the congenital type). The causes include sclerosis and fibrodegenerative changes within the conduction system, acute MI, drugs, endocarditis. Clinical features include syncopal episodes (Stokes-Adams attacks), varying systolic blood pressure, varying intensity of S_1, and intermittent cannon waves in the jugular venous pulse.
- First degree heart block and Mobitz type I block do not require any treatment. Mobitz type II and third degree heart block usually require pacemaker treatment in adults; atropine and isoproterenol may be used to increase the ventricular rate in the interim.

12.8 Rheumatic fever and valvular heart disease

ACUTE RHEUMATIC FEVER

Rheumatic fever is an immunological sequel to Group A β hemolytic streptococcal pharyngitis. The streptococcal throat infection is followed by a latent period before the onset of rheumatic fever. Rheumatic fever is important because heart disease frequently accompanies it.

Epidemiology The commonest age group affected by rheumatic fever is 5 to 15 years. Both sexes are nearly equally affected. Mitral valve disease and chorea are more common in females whereas aortic valve involvement is seen more often in males.

Overcrowding associated with low socioeconomic conditions is the most important predisposing factor since it may result in streptococcal cross-infections. From the Western countries, the incidence of rheumatic fever following streptococcal throat infection has been reported to be 3 per 1000 in the general population and 1–3 per 100 in crowded communities such as the army barracks. Extrapolation of the same figures combined with information on streptococcal pharyngitis available from the community surveys in India allows calculation of very rough estimates of the incidence of rheumatic fever in India (Table 12.25).

Etiopathogenesis Streptococcal pharyngitis precedes rheumatic fever. A strong association with group A β hemolytic streptococci is indicated by a number of observations (Fig 12.59).

Table 12.25 Estimated annual incidence of rheumatic fever in India

	Population
Total population of India (1991 census)	838×10^6
Population at maximal risk (5–15 years; 1991 census)	201.9×10^6
Sore throat episodes (1 episode/child/year)	201.9×10^6
Group A streptococcal infection (10% of all sore throats)	20.19×10^6
Conversion to rheumatic fever (0.3–3%, based on Western figures)	60,570-605,700

A history of preceding sore throat is available in approximately 50 per cent of patients. Case reports from literature of the pre-penicillin era are available, in which patients admitted to the hospital for rheumatic heart disease developed streptococcal pharyngitis followed by rheumatic fever. After penicillin became available, such cases were treated and eradication of streptococcal sore throat aborted the rheumatic fever episodes. Such cases illustrate the etiologic role of β hemolytic streptococcal throat infection in the development of recurrences of rheumatic fever, a role which is believed to be the same as its role in causing initial attacks of rheumatic fever. Similarly, epidemics of group A streptococcal throat infections in military training centres, and outbreaks of similar infection in schools, hospitals, and other closed population groups have been reported to be

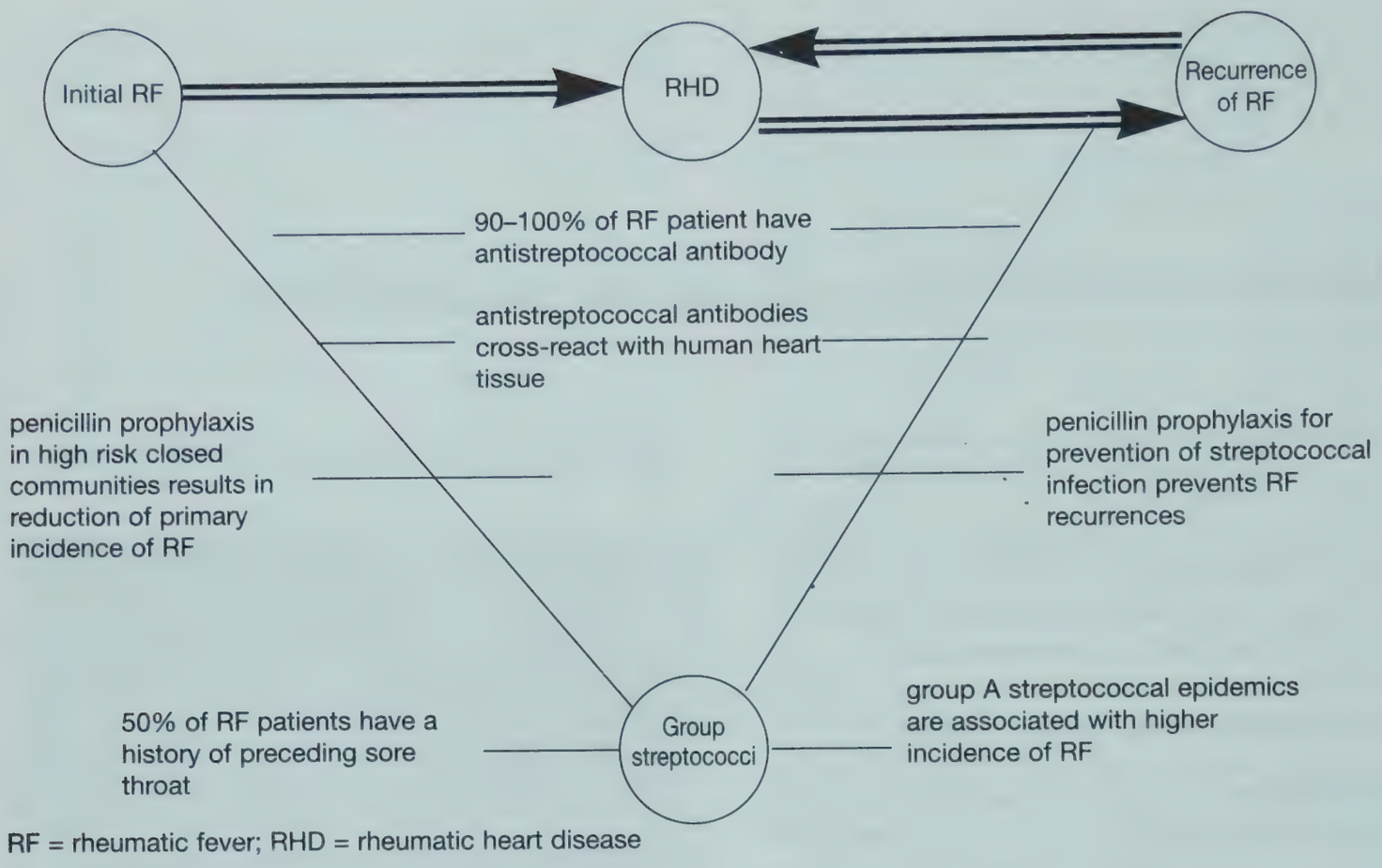


Fig 12.59 Factors which suggest an association of streptcoccal infection with rheumatic fever

associated with high incidence of rheumatic fever. Regular penicillin prophylaxis of military recruits in barracks known to have high incidence of streptococcal sore throat, dramatically reduced the incidence of rheumatic fever.

The high incidence of an elevated anti-streptolysin O titre in rheumatic fever patients indicates that they have had a recent streptococcal infection and thus provides important support for the hemolytic streptococcus hypothesis for the etiology of rheumatic fever. The antistreptolysin O titre is abnormally high in about 80 per cent of the patients. When the antistreptolysin O titre is not elevated, other antistreptococcal antibody tests are usually diagnostic.

Despite a definite association between streptococcal throat infection and rheumatic fever, streptococcal organisms have never been isolated from the joints, the heart or the blood stream. Following streptococcal sore throat there is a latent period of 10 days to several weeks before the onset of rheumatic fever. By the time rheumatic fever ensues, the evidence of streptococcal sore throat has also disappeared in the majority of cases, and the circulating antistreptococcal antibodies are the only telltale signs of the preceding infection. Considerable evidence now suggests that the rheumatic fever is an antigen-antibody reaction. It has been suggested that patients suffering from rheumatic fever produce antibodies against streptococcal cell wall and cell membrane proteins. The streptococcal antigen and human myocardium appear to be identical antigenically. It has been proposed that the cross-reactivity resides in the streptococcal M protein of the cell wall. There are 74 types of M proteins known and streptococci are classified accordingly. The streptococcal M protein has a characteristic α-helical coiled structure and can be considered

to have four distinct regions (A–D). Region A and B of the M protein show a resemblance to the myosin amino acid sequence. It has been demonstrated that the anti-streptococcal antibodies in human sera that cross-react with myosin recognise Gln-Lys-Ser-Lys-Gln sequence on the M protein molecule. Apart from M protein, another component of the cell wall is N-acetyl glucosamine; this too has been implicated in immunologic cross-reactivity with human connective tissue.

Although the streptococcal cell wall protein and carbohydrate has the capacity to produce antibodies capable of reacting with human connective tissue (resulting in rheumatic fever), this does not explain why some people are susceptible to the occurrence of rheumatic fever while others are not. It has been proposed that patients with rheumatic fever may be genetically programmed to respond abnormally to streptococcal infections. Many investigators have postulated an important role of inherited susceptibility in the causation of rheumatic heart disease. This observation is based on epidemiological surveys indicating occasional familial occurrence of the disease, correlation with certain blood groups and ABH secretions, and association with HLA antigens of major histocompatibility complex of humans. A higher frequency of HLA-DQw2 has been reported in patients with rheumatic fever. Also, a significant increase of HLA-DR3 and reduced frequency of HLA-DR2 has been reported in patients of Asian-Indian origin. Recent studies have revealed the existence of a genetically intricate system of serologically defined alloantigens that are selectively expressed on B lymphocytes; the homologous B cell alloantigen D8/17 has also been associated with rheumatic fever.

Pathology The pathological lesions of rheumatic fever may occur throughout the body in connective tissues around small blood vessels. The heart is the seat of the most characteristic lesions. All layers (peri-, myo-, and endocardium) of the heart are involved. Rheumatic pericarditis produces a serofibrinous effusion with shaggy deposits of fibrin on the epicardium, giving it an appearance as if a buttered sandwich has been pulled apart (hence called *bread and butter appearance*). Pericardial constriction has almost never been reported although calcification may occasionally be seen. Rheumatic myocardial involvement produces the most characteristic pattern of rheumatic activity.

Perivascular granulomatous lesions called *Aschoff nodules* (Fig 12.60) develop among more widespread swelling and fragmentation of interstitial collagen tissue.

Monohistiocytic infiltration in the interstitium and some myocyte degeneration may also be observed. Rheumatic endocarditis produces verrucous valvulitis (Fig 12.61) which leads to permanent deformity. These rheumatic vegetations are small and neither result in embolisation nor contain bacterial colonies as vegetations of bacterial endocarditis. Table 12.20 lists the characteristics of other forms of valvular lesions for comparison.

Although Aschoff nodules have almost invariably been described in the autopsies from patients dying of rheumatic carditis, such characteristic myocardial lesions occur in only 30–40 per cent of myocardial biopsies of patients presenting with primary or recurrent episodes of rheumatic fever. With time, the Aschoff bodies are eventually replaced by nondescript perivascular scars. Apart from the Aschoff lesions, non-specific inflammatory reaction in the edematous interstitial connective tissue is often observed. Varying degrees of myocyte degenerative changes have been noted. Neither characteristic Aschoff nodules nor non-specific interstitial or myocytic alterations have been found in the myocardial biopsies from the patients with chronic quiescent rheumatic heart disease.

Clinical features

Joint manifestations: Joint pain is of diagnostic

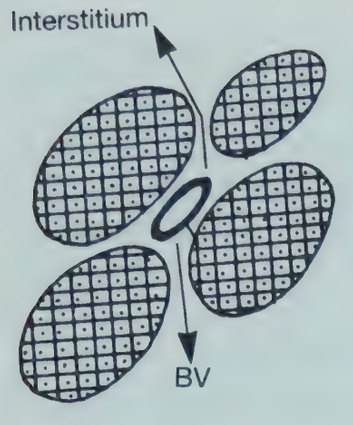
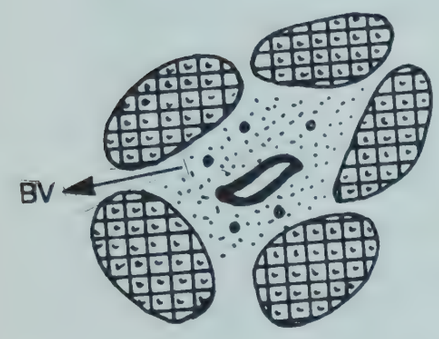


Fig 12.60 Development of the Aschoff body

Normal myocardium

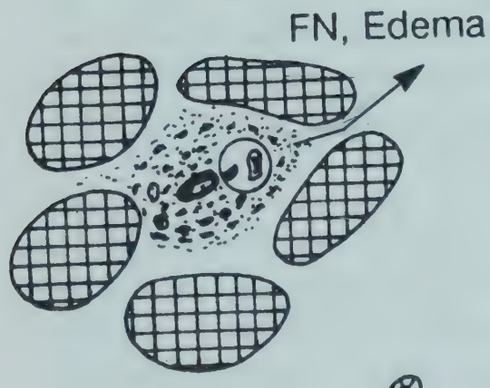
Aschoff lesions are found in the interstitium usually perivascularly (blood vessel = BV). Aschoff bodies develop through three stages. The intermediate stage is considered diagnostic of the rheumatic process and has not been reported in any other pathologic process.

Normal myocardium



Early (alterative, exudative or degenerative stage) <4 weeks

Edema of interstitial connective tissue and accumulation of basophilic acid mucopolysaccharides between collagen fibres which are pushed apart. Collagen fibrils subsequently undergo swelling, fragmentation and disintegration and acquire deep eosinophilic properties (fibrinoid necrosis = FN). Some plasma cells or lymphocytes can be seen.



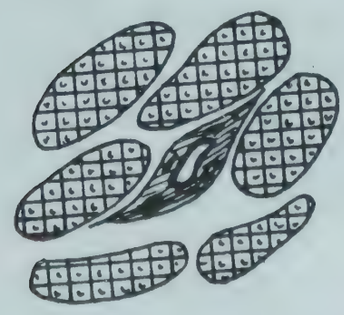
Intermediate (proliferative or granulomatous phase) 4–13 weeks

Within foci of FN, there is accumulation of cardiac histocytes (Anitschkow cell) or multinucleated histiocytes (Aschoff giant cells). There cells are intermixed with lymphocytes, plasma cells or PMN. The cells are arranged in a pallisading manner.

Anitschkow cells and Aschoff cells

Anitschkow cells (usually mononuclear) have a moderate amount of cytoplasm with vaguely defined borders. Nuclei are large and contain a prominent central chromatin mass. This chromatin in longitudinal section looks serrated (caterpillar-like) and in cross-section shows a halo about the chromatin bar (owl-eye appearance).
When multinucleated these cells are called Aschoff giant cells.

Myocytes/Muscle bundles



Late (fibrous or healing stage) 12–16 weeks

Regression of the proliferative component and disappearance of fibrous alteration coupled with fibrocytic invasion results in nondescript perivascular fibrosis.

importance because it is a frequent manifestation of rheumatic fever, and it nearly always occurs at the onset of the attack, thus calling attention to the patient's illness. Joint manifestations occur in upto 90 per cent of cases. Migratory polyarthritis occurs very commonly. Rheumatic arthritis generally involves larger joints such as the knees, ankles and elbows. Less commonly, smaller joints may also be involved. The younger the patient with acute rheumatic fever the less the arthritis and the older the patient the more the arthritis. In children, therefore, the joint symptoms are often mild. Even in these milder cases there is usually pain in at least two joints and examination of the patient may reveal tenderness or other objective evidence of joint involvement. When joint symptoms are due to rheumatic fever, there is nearly always fever and/or a rapid erythrocyte sedimentation rate. There should also be evidence of a recent streptococcal infection, best indicated by a high titer of antistreptolysin-O or other antistreptococcal antibody.

The pain and swelling of rheumatic arthritis appear rather quickly, last 3 to 7 days and subside spontaneously to appear in some other joint. Even in the absence of treatment, the involvement of each joint is short-lived, but the cumulative involvement of all joints is less so. Arthritis responds rapidly to aspirin. There is no residual damage to the joint.[1]

Cardiac involvement: Significant murmurs are the most common and the earliest clinical signs of carditis in acute rheumatic fever. Over 50 per cent of the patients with an initial attack of rheumatic fever have significant murmurs indicative of valvular involvement. Carditis is an early manifestation of rheumatic fever. Most of the patients who develop carditis do so within the first two weeks of the onset of rheumatic fever, and by the time a patient seeks medical attention evidence of carditis is already present.

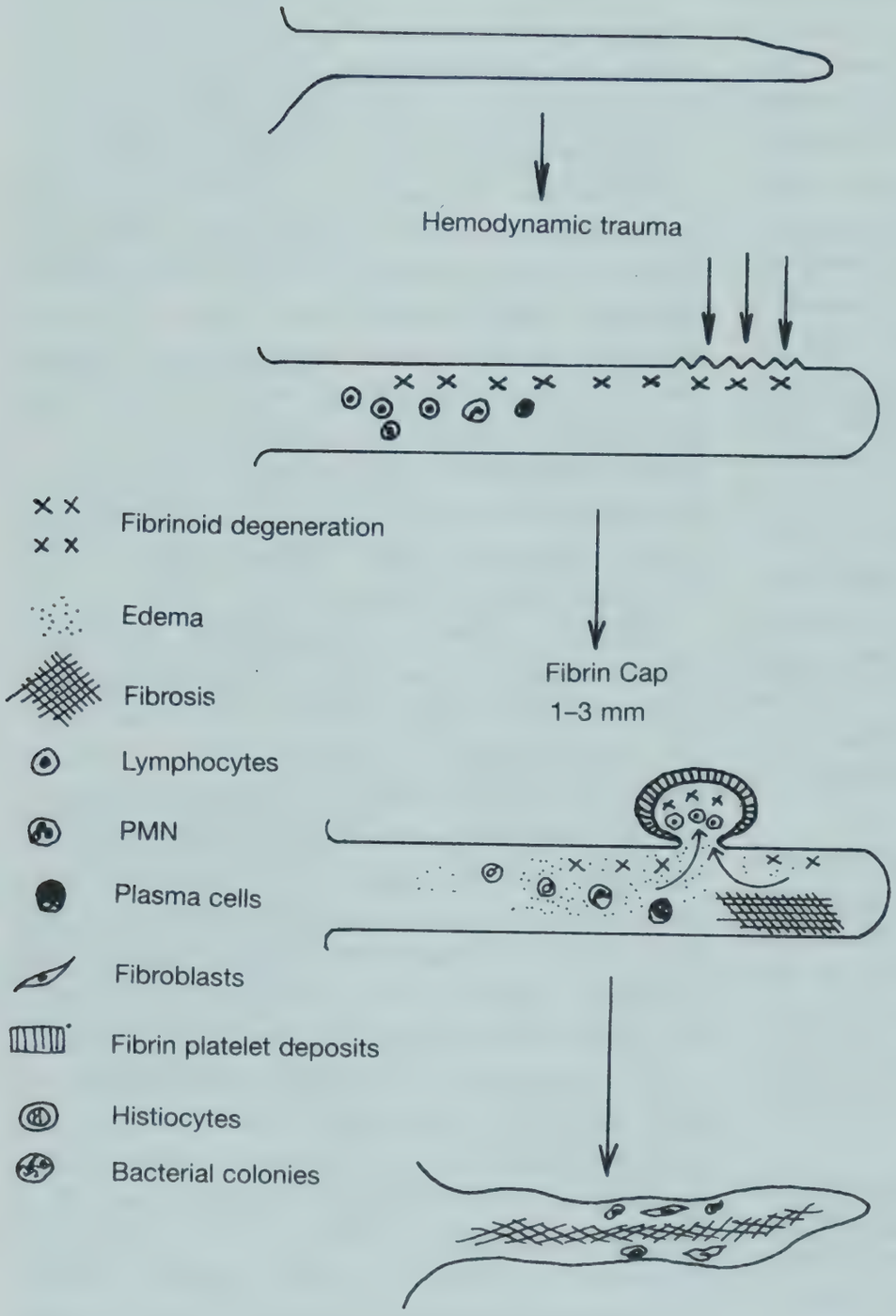
Rheumatic carditis is a pancarditis involving the endocardium, myocardium and pericardium. The endocarditis is represented by valvular regurgitation murmurs. The usual early signs are those of mitral regurgitation alone or mitral plus aortic regurgitation. The mitral valve is involved in all cases of rheumatic carditis on pathological examination. Clinically, almost 95 per cent patients have a mitral regurgitation murmur, a fourth of them also have an aortic regurgitation murmur. Only about 5 per cent of patients present with pure aortic regurgitation. Valvular stenosis also never occurs early. Tricuspid valve involvement occurs in 10 to 30 per cent of cases. Isolated tricuspid regurgitation as a manifestation of acute rheumatic fever does not occur. Pulmonary valve involvement in acute rheumatic fever is never seen.

Clinical evidence of pericarditis is seen in approximately 15 per cent of those who have carditis. Pericarditis results in precordial pain. On auscultation, a friction rub is present. Pericardial involvement in rheumatic fever is always associated with additional evidence of valvulitis which may be unmasked after subsidence of the pericardial rub. Rheumatic pericarditis is associated with only small effusions and does not produce tamponade. It does not result in constrictive pericarditis either.

The presence of rheumatic myocarditis is indicated by unexplained but unequivocal cardiac enlargement or congestive heart failure in children. The first heart sound may be soft, a third heart sound (S_3 gallop) may be present and sometimes a delayed diastolic murmur (*Carey Coombs murmur*) may be heard. Carey Coombs murmur does not indicate mitral stenosis (which never occurs early). Although other explanations have been suggested, it is most probably due to a prolonged S_3 that occurs during rapid inflow or a combination of S_3 and S_4. It tends to disappear after the myocarditis subsides.

In young people with rheumatic fever the development of congestive heart failure is almost always due to active rheumatic myocarditis in addition to valvular damage.

[1] A rare form of chronic deforming arthritis called *Jaccoud's arthritis* has been reported.



Normal valve with healthy endothelium tolerates hemodynamic trauma without any injury.

Initiation of the rheumatic process results in edema of whole valvular substance with cellular infiltration of predominantly lymphocytes. Fibrinoid change occurs near the surface of the valve which has become susceptible to hemodynamic trauma at valve closure lines.

Traumatised valvular surface attracts fibrin and platelets. A fibrin cap is formed. Degenerated valve substance is extruded out to produce a tiny vegetation.

No bacterial colonies are encountered in vegetations. Vegetations are tightly adherent to valve surface and do not embolise. The inflamed valve heals with deformity giving rise to stenosis/regurgitation.

Fig 12.61 Rheumatic valvulitis: pathologic evolution

These patients always have significant murmurs and, not infrequently, pericarditis. In very young children, the first apparent change marking the development of heart failure may be swelling of the face. When the puffiness is marked, it may resemble that seen in nephrosis.

For the diagnosis of rheumatic carditis in the initial attack of rheumatic fever, one needs to establish the presence of endocarditis, pericarditis or myocarditis. For the recurrence of active carditis, demonstration of an unequivocal change in the previous cardiac status is advised. Such a change can be demonstrated by the appearance of a new murmur, or an interval

Table 12.26 Forms of valvular lesions

Type	Etiology	Appearance/Location	Microscopy		Embolic potential	Bacterial colonisation	Valve destruction
			Valve	Vegetation			
1. Marantic	requires coagulability of blood (as in cancers) and degenerative/sclerotic valvular changes	usually multiple <3 mm occasionally single large (larger than RF always) on atrial surface of atrio-ventricular, valves, ventricular surface of semilunar valves, not on mural endocardium, not in valve pockets, M>A>T	swollen collagen, fibrinoid change underneath vegetation inflammatory cells rare	degenerative collegen with serum, fibrin and platelets	high	none but may serve as nidus for SBE	no
2. Atypical (Libman-Sack's)	in <50% patients with SLE	flat, granular (larger than RF) on both surfaces M and T may occur in pockets, mural endocardium on chordae/papillary muscles generally more than 1 valve	edema, fibrinoid change with histiocytes-lymphocytes; *Hematoxylin* bodies are characteristic (clumps of bodies in bone marrow) proliferation of endothelium and neovascularisation with inflammation	fibrinoid and necrotic zones associated with fibrin and platelets	no	none but may serve as nidus for SBE	no
3. Bacterial Acute Subacute	acute caused by more invasive/destructive organisms such as staphylococci (during skin/renal/lung infections, cardiac/non-cardiac surgery or iv drug abuse) occur on normal valves; subacute caused by less virulent organisms (such as streptococcus viridans), occur during transient URI or dental/ genitourinary manipulation, underlying valvular deformity required (RHD 50%, congenital 20%)	friable, variable size, atrial surface of atrio-ventricular valves, ventricular surface of semilunar valves spread along valve surface, pockets predominantly M>A, right side rare	non-specific inflammatory reaction; acute has more polymorphonuclear reaction and abscess formation; in subacute form underlying valve deformities are obvious	fibrin/platelets leukocytes + prominent bacterial colonies	high	always	yes

M = mitral valve, A = aortic valve, T = tricuspid valve, RF = rheumatic fever, SBE = subacute bacterial endocarditis

change in the preexisting murmur(s). It can also be represented by an obvious increase in the previous cardiac size. Unexplained recent onset of congestive heart failure, although suggestive of rheumatic activity needs to be differentiated from the hemodynamic deterioration resulting from naturally progressive valvular damage.

Skin manifestations: **subcutaneous nodules and erythema marginatum :** Subcutaneous nodules appear most commonly over bony prominences such as the olecranon process and the lateral condyles of the elbow, the edges of the patella, the occiput, and the tips of the spinous processes over the back; they are sometimes attached to tendons such as the flexor tendons of the palm. They are not attached to the underlying bone. They are non-tender structures that vary in size from that of a pinhead to that of an almond. Unless looked for meticulously, they are often easily missed. These nodules are clinically indistinguishable from those of rheumatoid arthritis but the nodules of rheumatic fever are generally confined to children. Subcutaneous nodules in rheumatic fever usually do not appear until three to six weeks after the onset of the attack, and may not be helpful in making an early diagnosis. They are, however, an important confirmatory sign. They last from a few days to weeks but have been known to last for as long as an year; they disappear rapidly after initiation of corticosteroid therapy. Nodules are seen in about 10 per cent of patients with an initial attack of rheumatic fever, but in patients with significant murmurs the incidence is about 20 per cent. Nodules are a sign of severe rheumatic fever and when nodules are multiple, valvular involvement is almost invariable.

Erythema marginatum is an early manifestation of rheumatic fever. Although considered to be more specific than other varieties of skin manifestations, erythema marginatum is known to be extremely rare in Indians, possibly because of the dark complexion of the skin. Erythema marginatum is an evanescent, pink or faintly red, circinate, non-itching rash. The coloured margins are usually thin and the clear centres are relatively large. The lesions, which are quite variable in size and number, are usually macular but, when extensive, they may be very slightly raised. It occurs on various parts of the body, is predominantly seen over the trunk, but practically never on the face. It has been reported in about 10 per cent of patients in western literature. The incidence of significant murmurs indicative of valvular involvement is about 70 per cent in patients presenting with this rash.

Neurologic manifestations of rheumatic fever (Sydenham's chorea): Chorea is characterised by purposeless, jerky, involuntary movements. It is usually generalised but is sometimes predominantly one-sided. It may involve the face, and may result in deranged speech. Muscular incoordination results in awkward gait; the posture of the outstretched hands in chorea characteristically shows a typical *'silver-fork' appearance*. The handwriting may be totally illegible and may steadily improve over time. Handwriting, therefore, may be a good objective way of following the progress of patients with chorea. The affected child may be emotionally disturbed. When left untreated, chorea has a self-limiting course; its duration is variable and ranges from two to six weeks, but it is never permanent.

Chorea may either occur alone or may be associated with other manifestations of rheumatic fever.

Pure chorea in children is almost always due to rheumatic fever. When chorea occurs in patients with other stigmata of rheumatic fever, the involuntary movements generally do not develop until about three months after the onset of acute rheumatic fever, and by this time more acute signs of illness have subsided, and the signs of systemic inflammation or preceding streptococcal infection have returned to normal. Chorea is usually confined to childhood and is extremely rare after 20 years of age in either sex. Chorea is more common in women than in men.

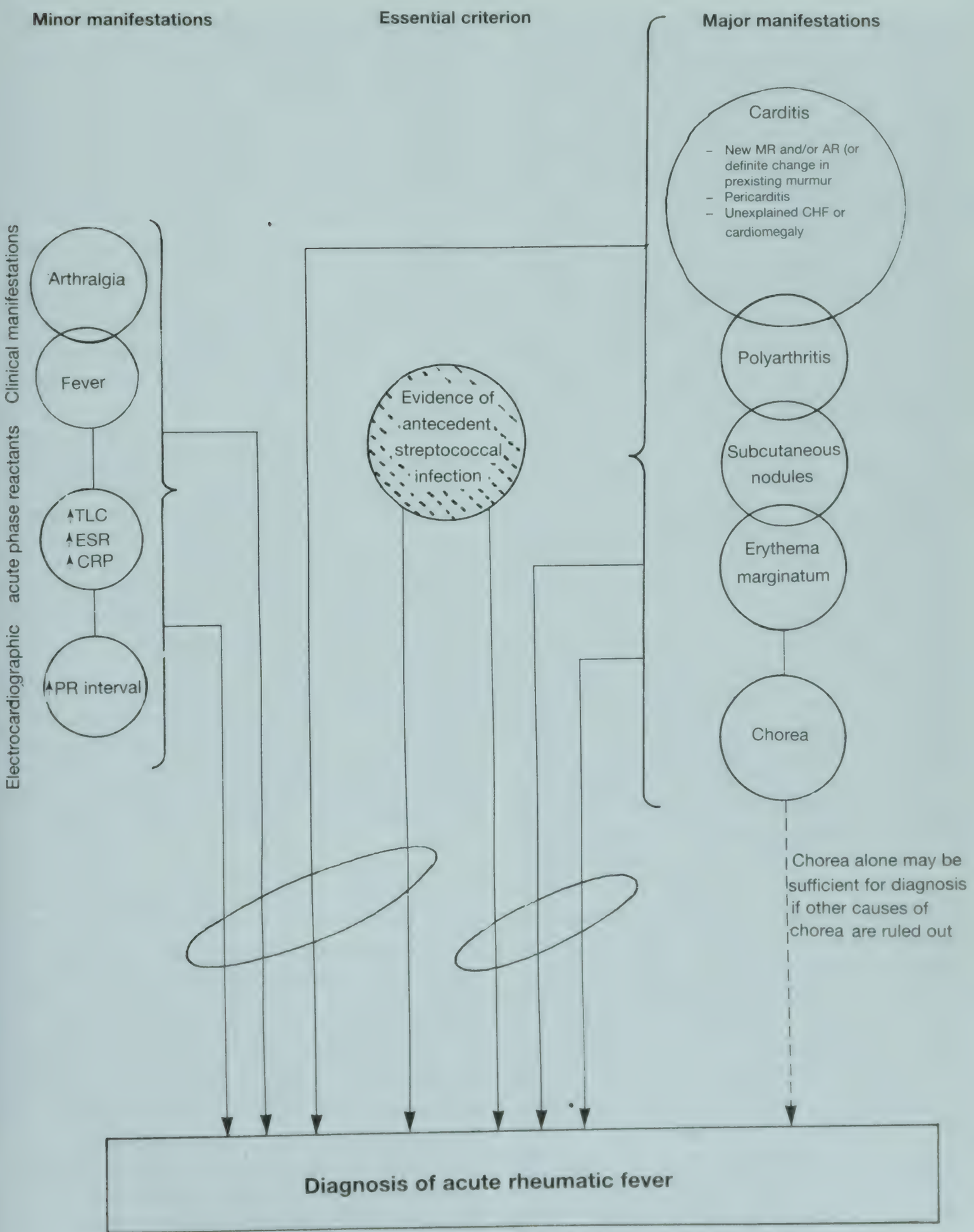


Fig 12.62 Jones criteria (Update 1992) for the diagnosis of rheumatic fever

Diagnosis Guidelines for the clinical diagnosis of acute rheumatic fever, originally suggested by T. Duckett Jones, have been subsequently revised three times by the American Heart Association. The manifestations of rheumatic fever have been divided into *major* and *minor* categories. The *major manifestations* offer the least likehood of improper diagnosis and include arthritis, carditis, subcutaneous nodules, erythema marginatum and chorea. *Minor manifestations,* although suggestive of rheumatic fever, are not in themselves sufficient for the diagnosis of rheumatic fever. Minor manifestations include some less important clinical signs (arthralgia without objective evidence of joint involvement, and fever), signs of systemic inflammation like elevated erythrocyte sedimentation rate and C-reactive protein, as well as prolonged electrocardiographic PR interval. The preceding evidence of streptococcal sore throat as suggested by antistreptococcal antibodies constitutes *supportive evidence.*

Two major criteria, or one major and two minor criteria are required for the diagnosis of rheumatic fever. In addition, demonstration of preceding evidence of streptococcal infection is essential for diagnosis (Fig 12.62). The presence of the essential criterion is not required in chronic manifestations of rheumatic fever like chorea and insidious onset of rheumatic carditis or chronic carditis. These guidelines are applicable for the initial attack of rheumatic fever. Strict application of these criteria is not recommended in patients with preexisting rheumatic heart disease, and the physician is encouraged to use clinical judgement in making a diagnosis. It is perhaps, less complicated to consider the diagnosis of rheumatic fever when one or more of the following are present: poststreptococcal arthritis, poststreptococcal carditis or chorea.

Evidence of recent streptococcal infection: The most useful information regarding recent infection is obtained by the high serum titres of antistreptococcal antibodies, and antistreptolysin (ASLO) antibody is the most commonly employed antibody estimation. Elevated levels of ASLO only indicate previous streptococcal infection and not rheumatic fever, although the higher the level, the more the likelihood of recent streptococcal infection. However, normal ASLO titres do not necessarily exclude a recent streptococcal infection. Rising titre of ASLO is a strong evidence for a recent streptococcal infection. ASLO titres are diagnostically high in about 80 per cent of patients. If three antibodies are assessed, the likelihood of the diagnostic yield rises to about 95 per cent.

Obtaining a positive throat culture for streptococci is relatively uncommon when a patient presents with acute rheumatic fever. Conversely, a positive throat culture alone cannot be considered diagnostic of rheumatic fever. Residua of scarlet fever in the form of desquamation of skin of the palms and soles indicates that the patient has had recent scarlet fever. Scarlet fever is rare in India.

Electrocardiographic and echocardiographic features: Prolonged PR interval has also been proposed as a manifestation of rheumatic carditis. Since many infections and a variety of cardiac conditions may cause prolongation of the PR interval, this finding is not specific for rheumatic fever. On the other hand, the incidence of an abnormally long PR interval in rheumatic fever is considerably greater than that observed in other diseases and this electrocardiographic manifestation may be of value in the diagnosis of rheumatic fever. The prolongation of the PR interval, however, is as common in patients without significant murmurs as those demonstrating significant murmurs. Therefore, this manifestation has no apparent significance with regard to the development of valvular damage. The electrocardiogram may also show ST and T wave changes. Doppler examination can be of help in identifying mitral, or mitral and aortic regurgitation. Pericardial

involvement can also be detected by echocardiographic demonstration of a small pericardial effusion.

Treatment There is no specific treatment of rheumatic fever and the management is symptomatic, combined with immunosuppressive therapy.

Supportive treatment: It has been customary to prescribe bed rest for all patients with acute rheumatic fever. Patients who do not have cardiac involvement can be ambulatory as soon as the joint symptoms subside, often in two to three weeks' time. In patients with carditis, bed rest is recommended till the evidence of rheumatic activity subsides. Salt restriction is recommended when congestive cardiac failure is present. The management of congestive cardiac failure is detailed in section 12.5.

Eradication of residual streptococcal infection: If the patient is not already on penicillin (primary episode of rheumatic fever or non-compliance with the previous recommendation in the patient with recurrence of rheumatic activity), therapeutic dosage of penicillin should be given (procaine penicillin 400,000 units, intramuscularly, twice daily (for 10 days) after throat cultures have been obtained. Subsequently secondary prophylaxis with long acting penicillin should be initiated or regularised.

Immunosuppressive therapy: Aspirin or corticosteroids are used for immunosuppressive therapy. Use of one or the other of the two agents, however, can be debated. Adrenocortical hormones have been shown to be life-saving in critically ill patients with severe carditis. Although the hospital prognosis appears to be significantly better with steroids in such patients, there is no literature available to suggest that the use of steroids will lessen or prevent valvular damage on follow-up, as compared to aspirin. Worsening of congestive heart failure occurs less often during steroid therapy. It has also been observed that fewer patients develop pericardial friction rub while on steroids. On the other hand, a new friction rub can still make its appearance, in spite of adequate doses of aspirin. Subcutaneous nodules also tend to disappear faster with the use of steroids as compared to aspirin. However, there is no difference in the morbidity or mortality in patients with mild carditis given steroids or aspirin. Neither is there evidence to suggest that steroids should be used in non-carditic patients. On the other hand aspirin results in dramatic relief of joint pains in patients with rheumatic arthritis. As a measure, if aspirin does not relieve pain in these patients, diagnosis of rheumatic fever should be reconsidered. Based on these data the following guidelines can be formulated:

If a patient has severe carditis with congestive cardiac failure steroids have to be used. In patients with carditis without congestive cardiac failure either steroids or aspirin may be used. However, if the patient does not have carditis aspirin should be given. Untreated rheumatic fever subsides by itself in 12 weeks in about 90 per cent of the patients; therefore, immunosuppressive therapy is given for 12 weeks. Full doses of aspirin are given for 10 weeks and then tapered off over the next two weeks, while full doses of prednisone are given for three weeks and then tapered very gradually over the next nine weeks. The steroid most commonly used is prednisone. The dose schedules are presented in Table 12.27.

Management of chorea Chorea, like any other feature of rheumatic fever, has a self-limiting course but does not result in residual deformity as cardiac involvement does. The patient should be provided complete physical and mental rest. While phenobarbitone (30 mg thrice daily) is predominantly prescribed, other drugs like chlorpromazine, promethazine or diphenhydramine can also be used for sedation. Steroids can be used in patients who do not respond adequately to a combination of chlorpromazine and phenobarbitone, especially if they had

Table 12.27 Recommended schedule for the treatment of rheumatic fever

Aspirin		*Prednisone*
90–120 mg/kg/day in 4 divided doses or to ensure blood levels of 25–30 mg/dl for 10 weeks	Week 1	
	Week 2	60 mg p.o.*
	Week 3	
	Week 4	50 mg p.o.
	Week 5	40 mg p.o.
	Week 6	35 mg p.o.
	Week 7	30 mg p.o.
	Week 8	25 mg p.o.
	Week 9	20 mg p.o.
	Week 10	15 mg p.o.
taper in 2 weeks	Week 11	10 mg p.o.
	Week 12	5 mg p.o.

* 40 mg p.o. in case of children <20 kg weight

evidence of elevated acute phase reactants and ASLO at admission.

Prognosis Prognosis of rheumatic fever and rheumatic carditis prior to the use of penicillin and adrenocorticosteroids is best exemplified by the 20-year follow-up study of 1000 patients by Bland and Jones from the House of Good Samaritan, Boston, U.S.A. On admission 653 (65%) patients had cardiac involvement and 347 (35%) had none. By the end of 20 years, 301 patients had died and nearly all of these were those who initially had cardiac involvement. This poor prognosis contrasts with the good prognosis after the use of penicillin started in 1945. There was a marked decrease in mortality and marked increase in disappearance of cardiac murmurs.

Long term follow-up studies in patients who initially had chorea alone have shown the appearance of heart disease in 20 per cent of patients over twenty years, and in 30 per cent of patients over thirty years. This suggests that such patients must have suffered from subclinical carditis or had mild undiagnosed carditis which had subsided by the time the patient presented with chorea.

Prevention It can be appreciated from the foregoing discussion that prevention of the streptococcal infection is mandatory for prevention of recurrences of rheumatic fever. Secondary prevention can best be provided by long-acting benzathine penicillin. The dose is 1.2 mega units once every 3 weeks (or 0.6 mega units every alternate week in pediatric patients). Ideally, penicillin prophylaxis should continue lifelong. This recommendation is most essential for those presenting with carditis. In patients without carditis, 5–10 years of prophylaxis from the last attack of rheumatic fever or until the patient reaches 25 years of age (whichever occurs later) is suggested as adequate.

Primary prophylaxis of rheumatic fever can be obtained by prevention of streptococcal infection before rheumatic fever has occurred.

Although no recommendations for such prophylaxis are yet available, this should be the ultimate goal if rheumatic fever has to be eradicated. Isolated reports of treatment of all sore throats have resulted in decline in the incidence of rheumatic fever. Treatment of all sore throats, however, may neither be practical nor economical. Another strategy could be the identification and treatment of only streptococcal sore throats or identification of high risk individuals and treatment of their sore throats. Rapid identification techniques for streptococci are now being developed which recognise group A streptococcal polysaccharides obtained from throat swabs within a matter of minutes. On the other hand, high risk individuals can probably be recognised by suceptibility tests like the B cell alloantigen D8/17 or other better markers yet to be investigated.

Primary prophylaxis can best be achieved if a vaccine is created for streptococcal infection (rheumatic fever vaccine). The development of such a vaccine suffers from some technical problems. M protein is the virulent factor, and there are about 74 M types, almost any of which can result in rheumatic fever. The vaccine, therefore, needs to be polyvalent. Furthermore, since there is cross-reactivity between cardiac myosin and M proteins, there is always a fear of development of anti-heart antibodies. Scientists are now proposing to construct amino acid sequences from C and D regions of the M protein and link them with tetanus/cholera toxins or vaccinia. C and D regions are homologous in all types of M proteins and do not cross-react with at least intact myosin molecules. However, it still remains to be seen whether less immunogenic C and D portions will evoke adequate immune response.

MITRAL STENOSIS

Mitral stenosis is defined as anatomic narrowing of the mitral valve orifice. The normal mitral valve has an area of 4–6 cm^2. Mitral valve areas of between 1.5–2.5 cm^2, 1–1.5 cm^2 and <1.0 cm^2 are indicative of mild, moderate and severe degrees of mitral stenosis, respectively.

Etiology Almost all the cases of mitral stenosis in adults are secondary to rheumatic heart disease. Rare causes include congenital mitral valve abnormalities (parachute mitral valve), and connective tissue disease (systemic lupus erythematosus).

Epidemiology Mitral stenosis is more common in females and occurs in the second decade of life. Unlike in Europe and America where mitral stenosis occurs in the third decade, in India valve stenosis may be encountered in young children (known as *juvenile mitral stenosis*).

Pathology Rheumatic mitral valve disease is characterised by contraction and scarring of valve leaflets, fusion of valve commissures, as well as by retraction and fusion of chordae tendineae. The mitral leaflets may calcify and become rigid and immobile. Pathologically, a '*fish-mouth*' orifice of the mitral valve is typical.

Pathophysiology and clinical features Mitral stenosis impedes diastolic filling of the left ventricle resulting in an increase in left atrial pressure. The elevated left atrial pressure is passively transmitted to the pulmonary veins, resulting in increased pressure in the pulmonary capillaries. This causes pulmonary congestion and initially manifests clinically as exertional dyspnea. When stenosis is mild, dyspnea occurs only with vigorous exertion. As stenosis becomes severe, dyspnea occurs on minimal exertion, and finally even at rest; orthopnea, and paroxysmal nocturnal dyspnea become prominent symptoms. Tachycardia due to any cause, and pregnancy can worsen symptoms of mitral stenosis. The high pulmonary arteriolar resistance leads to a decreased cardiac output; a low forward cardiac output manifests clinically

as fatiguability. Pulmonary arterial hypertension places an increased burden on the right ventricle (elevated afterload), which hypertrophies, dilates and eventually fails. Elevated right ventricular and right atrial pressure is transmitted passively to systemic veins; right heart failure ensues with peripheral edema, tender hepatomegaly, and ascites. Chest pain suggestive of angina may occur due to increased oxygen demand of the hypertrophied right ventricle coupled with a reduction in supply due to a low cardiac output or due to concomitant coronary artery disease (in middle-aged or elderly patients). Hemoptysis is a common symptom of mitral stenosis and may be related to several causes. Rupture of the broncho-pulmonary vascular connections that develop as a consequence of pulmonary venous hypertension is the most common cause. The sputum may be blood-stained, possibly due to pulmonary edema, chronic bronchitis (bleeding from a hyperemic mucosa) or pulmonary infarction. Hoarseness is an occasional complaint and is related to compression of the recurrent laryngeal nerve between the enlarged pulmonary artery and the aorta (*Ortner syndrome*).

As the left atrium dilates, atrial fibrillation may supervene. Stasis of blood within the dilated left atrium predisposes to thrombus formation and possible thromboembolism. Embolic episodes may present as neurologic deficits (due to embolisation of an artery supplying the brain) as abdominal or flank pain (due to embolisation

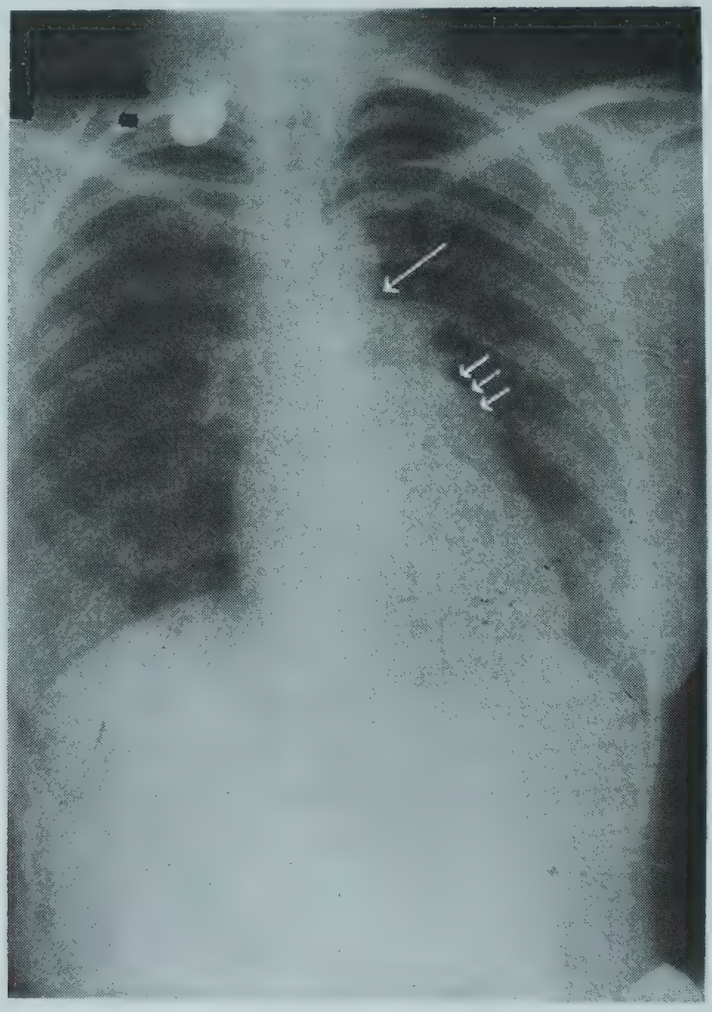


Fig 12.63 Plain X-ray chest (PA view) of a 30-year old woman with severe mitral stenosis. The left heart border appears straightened due to a prominent main pulmonary arrtery segment (single arrow) and an enlarged left atrial appendage (multiple arrows). There is moderate pulmonary venous hypertension reflected by upper lobe pulmonary veins that are more prominent that lower lobe veins (cephalisation)

of a splanchnic or renal artery) or as chest pain due to myocardial infarction (due to embolisation of a coronary artery).

The clinical examination reveals a small volume pulse; atrial fibrillation may be present. The jugular venous pressure may be elevated if right-sided cardiac pressures are raised. The cardiac apex is '*tapping*' (which reflects a palpable loud first sound) and a right ventricular 'lift' may be palpable along the left sternal border (which signifies right ventricular pressure overload). There may be diastolic thrill at the apex and the second sound may be palpable. Auscultation reveals a loud S_1 (loud M_1 or 'closing snap'), a loud P_2 (if pulmonary hypertension is present) and an *opening snap* (OS) occurring in diastole after A_2. The hallmark of mitral stenosis is a low-pitched diastolic rumble that begins with the OS and becomes loudest before S_1 (*presystolic accentuation*). The presystolic accentuation is more pronounced in sinus rhythm; it is heard even in atrial fibrillation but at the end of short diastoles (when left atrial pressure is still high). The rumble is best heard with the bell of the stethoscope with the patient in the left lateral decubitus position. The longer the duration of the murmur, the greater the severity of valvular stenosis. Sometimes in patients with severe mitral stenosis, severe tricuspid regurgitation and right-sided heart heart failure, the diastolic murmur may be inaudible because of a low forward cardiac output, the loud systolic murmur of tricuspid regurgitation and because the dilated right ventricle forms the apex. This condition is referred to as *'silent mitral stenosis'*. The OS is believed to be related to sudden tensing of the anterior mitral leaflet by the chordae tendineae after cuspal opening, and indicates valve mobility. The A_2-OS interval is a measure of the time taken by the mitral valve to open in diastole and is inversely related to left atrial pressure and the severity of stenosis. A systolic murmur may be heard and may reflect associated mitral regurgitation or indicate tricuspid regurgitation. A low-pitched soft decrescendo diastolic murmur may be heard in the pulmonic area and indicates pulmonary regurgitation (*Graham Steell murmur*) consequent to elevated pulmonary artery pressures. This murmur must be differentiated from the diastolic murmur of aortic regurgitation which is a more frequent accompaniment of mitral stenosis.

Investigations Electrocardiographic findings of mitral stenosis include left atrial abnormality (P mitrale), right axis deviation and right ventricular hypertrophy. Atrial fibrillation may be present and the fibrillatory wave tends to be large ('coarse'). The chest X-ray is typical. The cardiac silhouette is normal in size, the left atrium and the left atrial appendage are dilated and the pulmonary artery is prominent; this results in 'straightening' of the left heart border (Fig 12.63). A double shadow of the dilated left atrium is characteristic along the right heart border. Pulmonary vascular redistribution is almost invariably present in moderate to severe degrees of mitral stenosis; upper lobe pulmonary veins are dilated and Kerley B lines may be present. Fluoroscopy is often utilised in patients with pure mitral stenosis in order to assess for mitral valve calcification; this is important for management decisions.

Echocardiography is an important diagnostic tool that helps establish the diagnosis, quantify the severity, detect associated regurgitation and involvement of other valves, identify left atrial appendage clots (in patients with atrial fibrillation), and assess suitability of the valve for balloon valvotomy. Doppler ultrasound techniques may provide a better estimate of mitral valve area than cross-sectional echocardiography.[1] A transthoracic echocardiogram is sufficient; a transesophageal echocardiogram may be obtained (if available) to evaluate the

[1] Mitral valve area by Doppler ultrasound uses the '*pressure half-time*' method. Mitral valve area (cm^2) = 220/ atrioventricular pressure half-time (milliseconds).

left atrial appendage for thrombi better (prior to closed surgical valvotomy or balloon valvotomy).

Cardiac catheterisation in not routinely required in isolated mitral stenosis unless the patient is over the age of 45 years (in which case coronary arteriography is required to exclude coronary artery disease), has multivalvular disease, or if the severity of mitral stenosis is unclear. Exercise testing is used to evaluate pulmonary arterial and wedge pressures during exercise in patients with severe limiting symptoms but 'mild' stenosis on evaluation. Catheterisation helps to estimate pulmonary wedge pressures, assess pulmonary hypertension and calculate the valve area using the *Gorlin formula*.[1]

Management All patients with mitral stenosis require prophylaxis against infective endocarditis (see later) and against rheumatic fever if they are below the age of 25 years. If atrial fibrillation is present and is of recent onset, cardioversion may be attempted; if atrial fibrillation recurs after cardioversion or if it is of long standing, anticoagulation must be considered. Oral anticoagulants are preferable unless contraindicated, in which case aspirin should be used. Digitalis, beta-blockers or calcium channel antagonists are useful for controlling the ventricular rate in patients with atrial fibrillation. The patient with mitral stenosis must be evaluated for the presence of symptoms and for lesion severity.

1. Patients with mild symptoms and mild mitral stenosis can be followed up. Female patients should be counselled regarding the advisability of pregnancy at a time when the valve lesion is mild. If there is a history of recurrent systemic embolism, mitral-valvotomy must be considered even in the absence of other cardiac symptoms.
2. Patients with severe symptoms but mild mitral stenosis must be evaluated to determine the exact etiology of the symptoms; exercise testing in the cardiac catheterisation laboratory may be required.
3. Patients with moderate to severe mitral valve stenosis but minimal symptoms should be questioned carefully to ascertain if they are limiting their activities to avoid symptoms.
4. Symptomatic patients with moderate to severe mitral stenosis (mitral valve area <1.2 cm^2) are candidates for definitive therapy to relieve valve stenosis. Medical treatment should include dietary salt restriction, diuretics, beta-blockers to slow heart rate, and digitalis if there is right-sided failure.

Young patients with isolated mitral stenosis and mobile, non-calcific mitral valves without significant subvalvular deformity can be treated either with balloon valvotomy (BMV) or with closed mitral valvotomy (CMV). Both modalities have similar results and the choice is based on patient preference (BMV avoids a thoracotomy and a scar whereas CMV is relatively inexpensive) and physician experience. Pregnant women with symptomatic mitral stenosis can be treated with closed mitral commissurotomy; the procedure is preferably planned in the second trimester of pregnancy.

If the mitral valve is calcific, or there is significant subvalvular deformity, open mitral commissurotomy under cardiopulmonary bypass is the preferable option. If there is more than mild mitral regurgitation, mitral valve repair or replacement are therapeutic options, the choice of the procedure being based on the 'repairability' of the valve and the surgeon's experience with the technique.

MITRAL REGURGITATION

Mitral regurgitation is the retrograde flow of blood from the left ventricle into the left atrium through incompletely coapting mitral valve leaflets.

[1] Mitral valve area =

$$\frac{\text{cardiac output} \div \text{diastolic filling period}}{38 \times \sqrt{\text{mean pressure gradient}}}$$

Etiology Mitral regurgitation may be chronic or acute. Rheumatic valve damage is the most common cause of chronic mitral regurgitation in India. Other *causes of chronic mitral regurgitation* are papillary muscle dysfunction (usually ischemic), myxomatous degeneration of the valve leaflets with prolapse (mitral valve prolapse syndrome), mitral anular calcification, congenital heart disease (atrioventricular canal defects, cleft mitral valve, endocardial fibroelastosis), left ventricular dilatation (secondary to dilated cardiomyopathy) and hypertrophic cardiomyopathy. The *causes of acute mitral regurgitation* include ruptured chordae tendineae (infective endocarditis or myxomatous mitral valve), rupture of a head of a papillary muscle (usually in acute myocardial infarction), mitral valve perforation (infective endocarditis) and cardiac trauma.

Pathophysiology and clinical features Rheumatic mitral regurgitation results from valve leaflets which coapt incompletely due to scarring along with retraction, shortening and contraction of chordae tendineae. In mitral valve prolapse, one or both of the redundant (billowing) leaflets may prolapse into the left atrium during systole thereby interfering with valve competence. In papillary muscle dysfunction, the normal papillary muscle contracts during systole and pulls down the mitral leaflet on its side; the leaflet supported by the dysfunctional papillary muscle loses support and prolapses into the left atrium with consequent loss of coaptation of leaflets. In rupture of chordae tendineae, portions of the mitral valve are flail; complete apposition of the cusps is not possible and the flail-part of the leaflet deflects the regurgitant stream into the left atrium.[1]

In chronic mitral regurgitation the left ventricle ejects blood into the low pressure left atrium. This results in left atrial and left ventricular volume overload. Since the left atrium has time to dilate and accommodate the regurgitant volume, the result is a lower left atrial pressure and lesser degree of pulmonary congestion. A limited forward cardiac output is the other principal mechanism of symptoms in chronic mitral regurgitation. As regurgitation becomes severe, exertional dyspnea, orthopnea and episodes of paroxysmal nocturnal dyspnea appear. In response to elevated pulmonary capillary pressure, the pulmonary arterial pressure increases. The right ventricle may dilate and symptoms and signs of right-sided congestion appear. Onset of atrial fibrillation is common as the left atrium dilates. Since the degree of stasis of blood in the left atrium is less in mitral regurgitation compared to mitral stenosis, the risk of embolism also seems to be lower.

It is important to understand the pathophysiology of chronic mitral regurgitation because it has therapeutic relevance. The left ventricular ejection fraction can be misleadingly high or normal in the presence of underlying ventricular dysfunction as the left ventricle unloads into a low resistance chamber. After surgical treatment, the left ventricle faces an increased impedance (it loses the left atrium as an unloading chamber). Appropriate timing of the surgery is important as delayed intervention can lead to irreversible left ventricular dysfunction.

In acute mitral regurgitation, a sudden pressure and volume overload is imposed on the left atrium that does not have the time to dilate. Florid pulmonary edema results.

Chronic mitral regurgitation produces varied clinical features, in accordance with its varied pathological causes. Physical examination reveals a brisk but low volume pulse. On palpation, the apical impulse is displaced downwards and outwards. A systolic or, more

[1] The direction of the regurgitant jet depends on which leaflet is flail or prolapsing; flail or prolapsing anterior leaflets are associated with a posterior jet and vice versa. Rheumatic mitral regurgitant jets can be central, anterior or posterior.

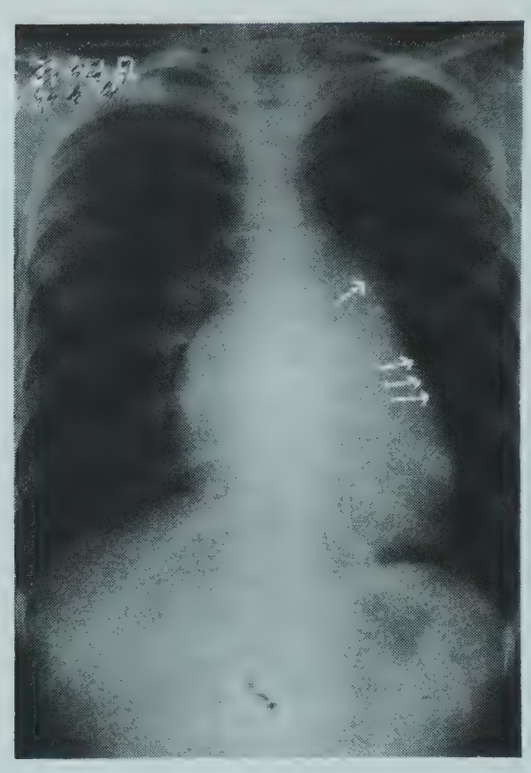


Fig 12.64 Plain X-ray chest (PA view) of a 35-year old man with severe MR and moderate TR. The pulmonary artery segment (single arrow) is delated. The left atrial appendage (multiple arrows) is enlarged. Note the presence of cardiomegaly (left ventricular type) and moderate pulmonary venous hypertension

commonly, a diastolic thrill and a third heart sound may be palpable. The first heart sound is generally soft (unless there is concomitant mitral stenosis) and the S_2 is widely split with a loud pulmonic component. An S_3 is usual in severe mitral regurgitation; absence of an S_3 suggests that the regurgitation is not severe. An S_4 in the presence of severe mitral regurgitation suggests ruptured chordae tendineae as the probable etiology. The hallmark of mitral regurgitation is a holosystolic murmur at the apex which usually radiates to the axilla. Patients with rheumatic mitral regurgitation often have signs of associated mitral stenosis. However, a diastolic murmur may occur in pure mitral regurgitation without indicating any valve stenosis; this murmur is loud and shorter, occurs in early diastole, often begins with a third heart sound and is related to increased flow across the mitral valve. The murmur that is produced by rupture of the chordae tendineae of the posterior papillary muscle is transmitted to the aortic area and the neck, thus simulating the murmur associated with aortic stenosis. Murmurs due to rupture of anterior chordae radiate to the spine and have a characteristic '*cooing*' quality. In patients with mitral valve prolapse there is typically a crescendo late systolic murmur that begins with a click; auscultatory signs often vary markedly with changes in the patient's position. The murmur of papillary muscle dysfunction is late systolic.

The patient with acute mitral regurgitation appears tachypneic and sick. The murmur of mitral regurgitation is harsh, and may radiate to the base.

Investigations Patients with rheumatic mitral regurgitation typically exhibit electrocardiographic left atrial enlargement; atrial fibrillation is common. Sinus rhythm is more likely to be preserved in non-rheumatic mitral regurgitation. The chest X-ray generally reveals enlargement of both the left atrium and the left ventricle, and signs of pulmonary venous congestion (Fig 12.64). On cross-sectional echocardiography, an

enlarged left atrium and a dilated hyperdynamic left ventricle are observed. Echocardiography may identify rheumatic mitral valve disease, mitral valve prolapse (holosystolic or late systolic prolapse of portions of the mitral valve), mitral anular calcification, scarred papillary muscles, vegetations, or flail leaflets (recognised by their extreme excursion into the left atrium in systole). The left ventricular size and function have prognostic significance. Colour Doppler ultrasound studies show the regurgitant jet well and provide a semiquantitative estimate of the severity of regurgitation.

Cardiac catheterisation reveals an elevated pulmonary capillary wedge pressure and a large regurgitant 'v' wave. Left ventriculography defines the degree of mitral regurgitation.

Management The primary goal of therapy of mitral regurgitation is reduction of left ventricular afterload. In acute mitral regurgitation this is achieved by the use of intravenous nitroprusside or intraaortic balloon counterpulsation. Early surgical intervention may be necessary in patients with acute mitral regurgitation.

In chronic mitral regurgitation afterload reduction can be achieved with oral vasodilators (converting enzyme inhibitors or hydralazine). In symptomatic patients with severe mitral regurgitation, surgery is advisable provided the left ventricular ejection fraction is greater than 40 per cent. Although surgery can be undertaken with lower values of left ventricular ejection fraction, postoperative morbidity may be significant; the decision of whether to operate or not is often individualised based on the preferences of the patient and the surgeon. Patients with asymptomatic severe mitral regurgitation must be followedup preferably on oral vasodilator therapy with regular monitoring of left ventricular function at 6 month intervals. Surgery must be considered in such an asymptomatic person if: 1) echocardiographic end-diastolic diameter is >75 mm, end-systolic diameter is >45 mm (26 mm/m^2) or fractional shortening is <30 per cent, or 2) at catheterisation the left ventricular ejection fraction is <60 per cent or the end-systolic volume is >60 ml/m^2.

The choice of the surgical procedure is based on the mitral valve morphology and the surgeon's experience and preference. Valve repair or replacement with a prosthetic valve are the two options. Myxomatous valves that prolapse are more often amenable to surgical repair than rheumatic valves.

Medical treatment consists of diuretics, vasodilators, digoxin and management of concomitant atrial fibrillation. Prophylaxis against rheumatic fever and against bacterial endocarditis must be instituted.

Mitral Valve Prolapse Syndrome

Mitral valve prolapse may be idiopathic or associated with heritable connective tissue disorders, such as Marfan syndrome and Ehlers-Danlos syndrome. The disorder appears to be more common in young women. Progression to severe mitral regurgitation is the most important complication of mitral valve prolapse and is most likely to occur in men above the age of 50 years. Cerebral embolism has also been associated with mitral valve prolapse.

AORTIC STENOSIS

The normal aortic valve (Fig 12.65) has a valve area of approximately 3–4 cm^2. Aortic stenosis represents narrowing of the aortic valve. Conventionally, an aortic valve area between 1–2 cm^2 is categorised as mild aortic stenosis, a valve area between 0.75–1 cm^2 (0.4– 0.7 cm^2/m^2) denotes moderate aortic stenosis, and a valve area less than 0.75 cm^2 (0.4 cm^2/m^2) denotes severe aortic stenosis.

Etiology The three principal causes of valvular aortic stenosis are congenital bicuspid aortic valve, senile degenerative aortic stenosis and rheumatic heart disease. A congenital bicuspid

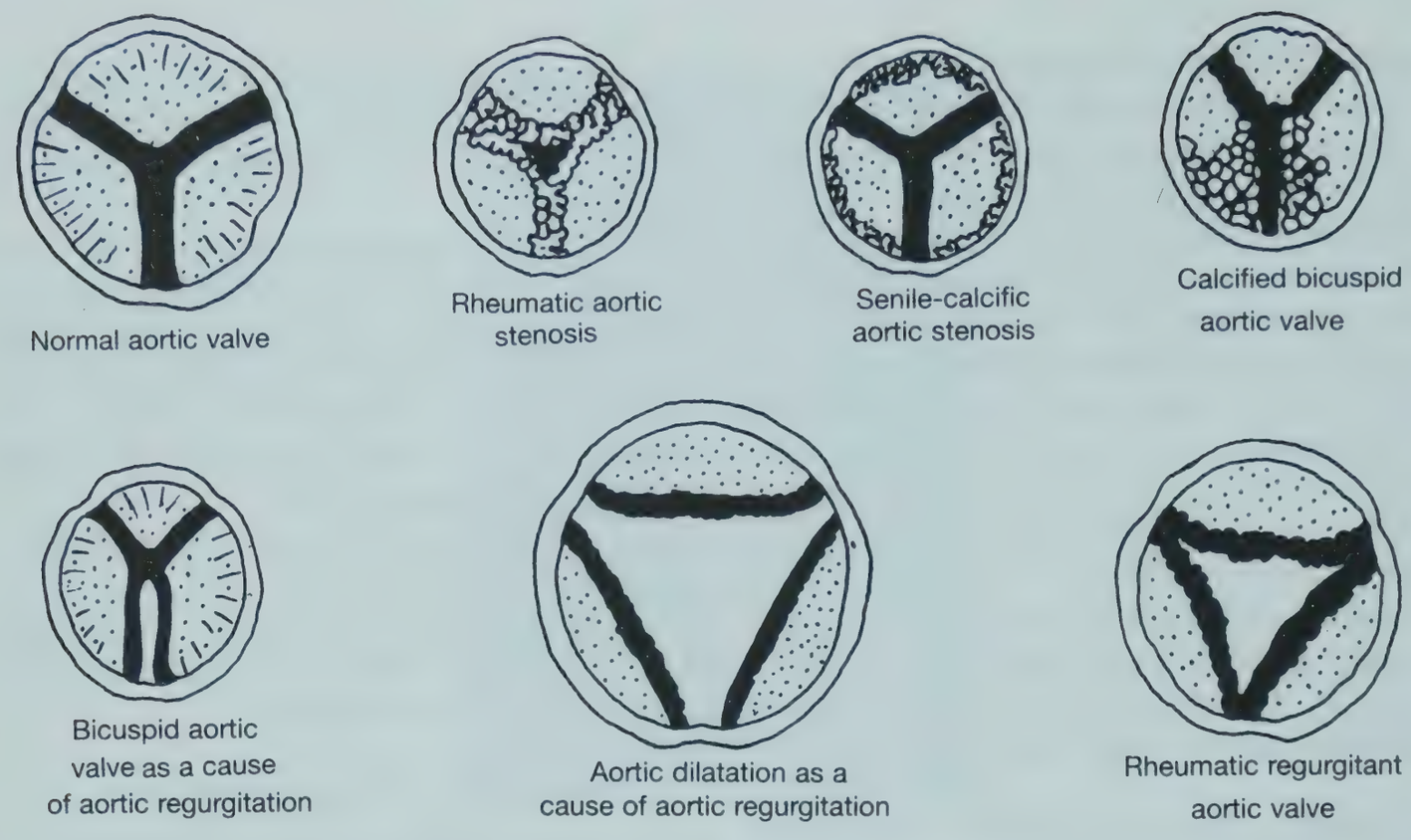


Fig 12.65 Pathology of aortic stenosis and regurgitation
The normal tricuspid aortic valve opens completely in systole and the cusps coapt in diastole. Bicuspid aortic valves can be stenotic when they fail to open completely or regurgitant when they fail to coapt fully in diastole. Rheumatic aortic stenosis is associated with commissural fusion; aortic regurgitation ensues when the cusps are fibrotic and shortened. Senile aortic stenosis is related to calcific degeneration of the valve cusps without primarily affecting the commissures. Aortic root dilatation can cause aortic insufficiency because the leaflets may fail to coapt fully and there may be commissural separation as well.

aortic valve can cause symptoms early in life, although it typically undergoes calcification in the fourth and fifth decades of life; calcification of the valve is associated with the development of hemodynamically significant stenosis. Rarer congenital anomalies of the aortic valve (such as a unicuspid aortic valve) can result in congenital aortic stenosis and symptoms in infancy. Rheumatic valvular aortic stenosis is uncommon and usually occurs in the presence of associated mitral valve disease; it is characterised by commissural fusion and thickening and fibrosis of valve leaflets. Degenerative aortic stenosis occurs in and beyond the sixth decade of life and is characterised by accumulation of calcium in the cusps of the valves, the commissures being spared.

Pathophysiology and clinical symptoms Aortic stenosis causes increased resistance to blood flow from the left ventricle. As a compensatory mechanism the left ventricle hypertrophies in order to maintain a normal forward cardiac output. The hypertrophied myocardium results in increased oxygen demand. It is also more stiff compared to the normal healthy myocardium (reduced compliance). The stiffer myocardium is more difficult to fill in diastole and the left atrial 'kick' becomes important for ventricular filling. Eventually, left ventricular diastolic pressure rises and is associated with elevation of left atrial pressure and increase in pulmonary capillary pressure.

The cardinal triad of symptoms of aortic stenosis is angina, syncope and heart failure. Angina may be related to the increased oxygen demands of the hypertrophied myocardium or to concomitant coronary artery disease. Syncope in aortic stenosis is usually related to physical exertion. Unlike the normal person, a person

with aortic stenosis has a relatively fixed forward cardiac output which does not increase with exercise. Syncope is triggered by the peripheral vasodilatation occurring during exercise. Occasionally, syncope in aortic stenosis may be due to ventricular or atrial arrhythmias. Signs of heart failure occur late in aortic stenosis and result from elevated left ventricular filling pressure. The triad of symptoms is also a guide to the prognosis of the subjects; the average survival after onset of angina is 5 years, after the onset of syncope is 3 years and after the onset of heart failure is only 2 years.

Physical examination Examination of the peripheral pulse can yield clues to the presence of significant aortic stenosis. The pulse has been termed *pulsus parvus et tardus,* which means a low volume pulse (reflecting a reduced pulse pressure) which is also additionally delayed (tardy). The carotid pulse shows a delayed upstroke and a prominent anacrotic notch at the time of peak turbulence across the valve. The cardiac apex is prominent and prolonged (sustained). The apex beat is not displaced in the absence of heart failure or concomitant aortic regurgitation. A left-sided fourth heart sound may be palpable. Auscultation reveals a diminished and delayed aortic component of the second heart sound. As the severity of aortic stenosis increases and left ventricular emptying is prolonged, the aortic component of S_2 may merge with the pulmonic component (rendering the second sound single) or may be heard after the pulmonic component (rendering the second heart sound paradoxic). A systolic click may be heard and signifies valve mobility (congenital bicuspid valve). A left-sided fourth heart sound may be heard and represents vigorous left atrial contraction. The hallmark of aortic stenosis is an ejection systolic murmur heard at the base, being maximal at the second right intercostal space. The murmur is harsh, crescendo-decrescendo, and its peak and duration depend on the severity of aortic stenosis. A longer murmur and a considerable delay in the peak of the murmur indicate a greater severity of stenosis.

Investigations The chest X-ray may reveal a prominent left ventricle (apex turned upwards and outwards), dilated ascending aorta (post-stenotic dilatation) and calcification of the aortic valve. Signs of pulmonary venous congestion may be present. The electrocardiogram may reveal left ventricular hypertrophy and left atrial enlargement. Echocardiography is the initial investigation of choice for evaluating the severity of aortic stenosis. The valves appear thickened and may appear domed in systole. The presence of two versus three cusps or commissural fusion can also be evaluated. Doppler echocardiography is the most important component and permits calculation of a 'peak gradient' across the valve using the modified Bernoulli equation.[1] The aortic valve area can also be calculated if the peak flow velocity below the aortic valve and the diameter of the left ventricular outflow can be measured accurately.[2] Cardiac catheterisation has remained the gold standard for assessment of aortic stenosis; the Gorlin formula[3] can be used to calculate the aortic valve area. However, in recent years the accuracy of Doppler echocardiography is being increasingly recognised and cardiac catheterisation is undertaken mainly for evaluating concomitant coronary artery disease (usually in individuals with angina or who are over 45 years of age).

Treatment Medical treatment of aortic valve stenosis (of any severity) consists of endocarditis prophylaxis prior to dental and surgical procedures. Patients with mild and moderate aortic stenosis are followed up medically with

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[1] Peak gradient = $4v^2$, where v is the peak velocity across the valve.

[2] This is also called the continuity equation:

$$\text{aortic valve area} = \frac{(V_{LVOT})^2 \times \pi/4_{(\text{LVOT diameter})^2}}{(\text{Peak velocity})^2}$$

[3] Aortic valve area = Cardiac output/Systolic ejection period/43.3 $\times \sqrt{\text{mean pressure gradient}}$

serial clinical and echocardiographic examinations. Treatment of severe aortic stenosis must be instituted prior to the onset of heart failure symptoms. Heart failure symptoms respond to digitalis, dietary salt restriction and cautious use of diuretics. The definitive treatment choices for severe aortic stenosis include valvotomy and valve replacement. Valvotomy may be achieved using a balloon catheter or with open heart surgery. The presence of severe calcification of the valve, concomitant coronary artery disease or significant aortic regurgitation indicate the need for surgical valve replacement. In young children with bicuspid aortic valves, balloon valvotomy is the treatment of choice. Adults generally require surgical valve replacement. Heart failure in patients with aortic stenosis responds well to surgical valve replacement, and recovery of left ventricular systolic function is usual.

AORTIC REGURGITATION

Aortic regurgitation (AR) is the retrograde flow of blood from the aorta into the left ventricle in diastole through incompletely closing aortic valve cusps.

Etiology Aortic regurgitation is caused by processes that affect the aortic leaflets or the aortic root. Rheumatic scarring and contracture of the aortic valve, congenital bicuspid aortic valve and valve leaflet destruction by bacterial endocarditis are common causes of aortic regurgitation due to a *primary pathology of the valve leaflets*. Systemic hypertension, seronegative spondyloarthropathies, Marfan syndrome and aortic dissection are conditions associated with aortic regurgitation due to a *primary pathology of the aortic root*; in these disorders, there is aortic root dilatation. Other uncommon causes of AR include syphilis, Takayasu's arteritis and ruptured sinus of Valsalva aneurysm. AR may be acute or chronic. Acute AR usually results from perforation of the valve leaflets in infective endocarditis or as a consequence of aortic dissection.

Pathophysiology In chronic AR, there is progressive volume overload of the left ventricle with a gradual increase in ventricular end-diastolic volume.[1] The gradual onset of AR permits left ventricular adaptation; left ventricular diastolic compliance is increased. Eventually, the dilated left ventricle fails. The rapid run-off of blood in diastole results in low diastolic blood pressure. The low diastolic pressure underlies the various physical signs of AR and also accounts for angina in this disorder (due to a lowering of diastolic coronary perfusion pressure).

In acute AR, there is an abrupt volume overload of the left ventricle which has no time to adapt; thus, the rapid onset of marked aortic regurgitation leads to a very high diastolic pressure in the left ventricle. The markedly elevated left ventricular diastolic pressure results in acute onset of heart failure.

Clinical features Chronic AR may be asymptomatic. When symptoms do occur, an awareness of heart beat is prominent and is related to a large stroke volume. Chest pain suggestive of angina may occur and tends to be nocturnal. Profuse sweating is common. Effort tolerance is preserved for years. Eventually, exertional dyspnea, orthopnea or paroxysmal nocturnal dyspnea develop. Acute AR presents as acute pulmonary edema. Acute severe chest pain is a prominent feature in acute aortic dissection.

Chronic AR can be recognised by the presence of the classic high-pitched decrescendo diastolic murmur and the peripheral arterial signs associated with the condition. The increased stroke volume results in increased systolic blood pressure. The widened pulse pressure has spawned a variety of signs with

[1] AR is associated with the largest hearts in cardiac pathology—*cor bovinum*.

eponyms; these include a slapping pulse that falls rapidly (*Corrigan's pulse*), head nodding (*de Musset sign*), pulsatile blanching and reddening of the nail capillary beds (*Quincke's sign*), pistol shot sounds over the femoral artery (*Traube's sign*), systolic murmur in the compressed femoral artery distal to the stethoscope and a diastolic murmur proximal to the stethoscope (to and fro *Duroziez murmur*), and systolic pressure in lower limb more than 20 mmHg higher than the arm systolic pressure (*Hill's sign*) are a few examples. A *bisferiens pulse* may be palpated over the carotids. Precordial palpation reveals a displaced and hyperdynamic apex beat and a diastolic thrill. The first heart sound and the aortic component of the second heart sound may be soft. In chronic AR there is a blowing, high frequency, decrescendo diastolic murmur that begins just after A_2 and extends through a variable portion of the diastole. A systolic murmur may be heard and usually indicates an increased stroke volume (rather than concomitant aortic stenosis). An *Austin Flint murmur* can often be heard; this is a low frequency mid-diastolic apical rumble due to turbulent flow across a mitral valve partially closed by the impinging regurgitant jet. The absence of an opening snap or a presystolic accentuation of the murmur, the presence of a soft S_1 and a hyperdynamic (non-tapping) apex beat enable the examiner to distinguish an Austin Flint murmur from one due to mitral stenosis. An audible third heart sound may be present in a patient with aortic regurgitation.

In acute AR, the patient appears sick, tachypneic and has tachycardia with marked peripheral vasoconstriction. The peripheral pulse pressure is normal and the murmur is short, soft and of a low frequency. The Austin Flint murmur is heard in early diastole to mid-diastole.

Assessing the severity of AR is more difficult than detecting its presence. The loudness of the diastolic murmur and the prominence of the peripheral arterial signs are less useful indicators of severity.

Investigations Electrocardiographic and roentgenographic signs of left ventricular enlargement are important guides to severity. The ECG reveals left ventricle hypertrophy and left atrial enlargement. The chest X-ray reveals an enlarged left ventricle with the apex displaced *down and out*. Marked dilatation of the aortic root suggests aortic root disease. Pulmonary venous congestion may be present. Colour Doppler echocardiography is the most helpful non-invasive test for aortic regurgitation. Echocardiographic evidence of AR include a characteristic diastolic flutter-like motion of the anterior mitral leaflet, and the visualisation of a turbulent regurgitant jet going backwards from the aortic valve into the left ventricle in diastole on colour Doppler flow imaging. The distance for which the regurgitant stream tracks into the left ventricle, and the diameter of the regurgitant jet at its origin are used for quantitation of its severity. Cardiac catheterisation with angiography is the most definitive means of assessing the severity of aortic regurgitation. Assessing left ventricular function in the presence of aortic regurgitation is a particularly important though difficult problem. The ventricle enlarges as a result of volume overload while continuing to function normally. Left ventricular filling pressure tends to remain normal in patients with aortic regurgitation, even when functional impairment is relatively advanced. Helpful indicators of left ventricular function are obtainable with echocardiography, radionuclide angiography or radiocontrast cineangiocardiography; these include the end-systolic volume and the left ventricular ejection fraction.

Treatment Aortic valve replacement is the treatment of choice for acute AR, chronic AR with symptoms of heart failure and chronic asymptomatic AR with evidence of reduction of left ventricular ejection fraction and cavity dilatation (echocardiographic left ventricular

end-systolic dimension > 55 mm, or ejection fraction < 0.55). Medical management of those with heart failure includes diuretics along with afterload reducing agents (vasodilators) such as captopril (ACE inhibitors) or hydralazine.

TRICUSPID VALVE DISEASE

Tricuspid Stenosis

Tricuspid stenosis (TS) refers to the narrowing of the tricuspid valve orifice with obstruction of flow from the right atrium to the right ventricle. The normal tricuspid valve has an area of 7–9 cm^2. When the valve area decreases to less than 2 cm^2, TS becomes clinically significant.

Etiology and pathophysiology TS is almost invariably due to rheumatic heart disease. Rarely, large tricuspid valve vegetations or a right atrial myxoma may occlude the tricuspid orifice resulting in functional stenosis of the valve.

TS results in the elevation of right atrial pressure. The right atrium becomes hypertrophied and distended while the right ventricle remains underfilled. Elevated right atrial pressure is passively transmitted backwards to the systemic veins; passive venous congestion of the liver results.

Clinical features The symptoms of TS include right upper quadrant abdominal discomfort and fatigue. Physical examination reveals a prominent 'a' wave in the jugular venous pulse and a flat 'y' descent. The murmur of TS is a high frequency rumbling mid-to-late diastolic murmur that intensifies during inspiration. An opening snap may be heard and presystolic accentuation may be prominent in sinus rhythm. There is a tender hepatomegaly with palpable presystolic pulsations. Tricuspid regurgitation of a variable degree usually coexists with TS.

Investigations The ECG reveals tall peaked 'P' waves (P tricuspidale) and, on occasion, atrial fibrillation. The chest X-ray shows a dilated right atrium, and a prominent superior vena cava. Echocardiography reveals a thickened and domed tricuspid valve and presence of a significant diastolic gradient across the tricuspid valve. Cardiac catheterisation is the definitive diagnostic test; an end-diastolic gradient of ≥ 2 mmHg across the valve is diagnostic.

Management TS is usually found in the presence of other rheumatic valvular heart disease and treatment is often dictated by these concomitant valve lesions. It is important to diagnose TS because if the lesion is not recognised and surgery is performed for other valve lesions, the patient is not likely to do well postoperatively. Surgical or balloon valvotomy have both been used with success to relieve TS.

Tricuspid Regurgitation

Tricuspid regurgitation (TR) is defined as the retrograde flow of blood from the right ventricle into the right atrium due to inadequate apposition of the tricuspid valve leaflets.

Etiology and pathophysiology TR is usually secondary to right ventricular dilatation, with or without concomitant pulmonary hypertension. With right ventricular dilatation, the tricuspid valve annulus also dilates and the valve becomes regurgitant. The causes of *TR with pulmonary hypertension* include any left-sided cardiac pathology (rheumatic and non-rheumatic mitral valve disease, left ventricular cardiomyopathies), primary pulmonary hypertension and cor pulmonale. The causes of *TR with normal pulmonary arterial pressures* include Ebstein's anomaly of the tricuspid valve, tricuspid valve endocarditis, trauma, carcinoid heart disease, tricuspid valve prolapse, right ventricular cardiomyopathy and atrioventricular canal defects.

TR results in elevated right atrial pressures and right atrial volume overload.

Clinical features Patients with TR complain of low cardiac output symptoms such as fatiguability. The symptoms of elevated systemic venous pressures include right upper quadrant tenderness (due to hepatic congestion), peripheral edema, and nausea and vomiting (splanchnic congestion).

The physical examination reveals distended jugular veins with prominent 'V' waves and 'y' descents; there are systolic hepatic pulsations synchronous with the systolic 'v' waves. Precordial palpation reveals a systolic thrill and a right ventricular heave. A loud pulmonic component of the second heart sound may be heard if there is associated pulmonary hypertension on auscultation. A right ventricular third heart sound is also common. The murmur of TR is high frquency, pansystolic and most prominent along the lower left sternal border. The murmur increases on inspiration (*Carvallo's sign*).

Investigations The ECG may show varying degrees of right ventricular volume overload depending on the severity of TR, tall P waves (P pulmonale) or a Qr pattern (indicative of right atrial enlargement in presence of right ventricular hypertrophy); atrial fibrillation may be present. The chest X-ray reveals enlargement of the right atrium and the right ventricle, often along with prominence of the superior vena cava. Doppler echocardiography is the investigation of choice; the severity of regurgitation can be estimated and the pulmonary arterial systolic pressure estimated using the simplified Bernoulli's equation.[1]

Management The treatment of TR depends on the underlying cause. Medical treatment consists of diuretics and sodium restriction. In cases of severe TR, a procedure such as tricuspid annuloplasty or repair may be required.

[1] Pulmonary artery systolic pressure = right ventricular systolic pressure = 4 (v^2) + right atrial pressure, where v = TR jet velocity; right atrial pressure can be estimated from the jugular venous pressure

INFECTIVE ENDOCARDITIS

Endocarditis is defined as an infection of the heart valves or of the non-valvular endocardium. Traditionally, it has been customary to distinguish a 'subacute' form of endocarditis from an acute form. Subacute bacterial endocarditis evolves over weeks to months, is caused by less virulent organisms (usually streptococci), affects valves with prior disease and has a clinical course which lasts for more than 6 weeks. Acute bacterial endocarditis, on the other hand, evolves over days to weeks, is caused by more virulent organisms (often staphylococcal species, affects healthy valves and runs a short hectic clinical course. However, it is being increasingly realised that the same organism may cause either pattern depending on whether it is hospital- or community-acquired, the type of valve affected (native versus prosthetic) and other host characteristics (such as intravenous drug abuse). Hence it is preferable to classify endocarditis along these lines rather than as acute or subacute. The term infective endocarditis is preferable. In this section, however, a reference to the traditional terms shall be made as they are still commonly used by physicians.

Epidemiology

The incidence of infective endocarditis has not changed over the last three decades, although the pattern of infection has changed considerably. In developed countries, the mean age of the patient with endocarditis has increased (i.e., the elderly are more affected), there is an increased incidence of right-sided endocarditis and gram-negative organisms are more often being implicated as compared to the past. Although the incidence of predisposing conditions like rheumatic valvular heart disease is decreasing in developed countries, the

increasing prevalence of invasive medical procedures and of intravenous drug abuse has served to compensate. There is also an increase in the incidence of prosthetic valve endocarditis in recent series.

Etiology Bacteria are the commonest organisms that cause endocarditis; streptococci and staphylococci species account for more than 80 per cent of all endocarditis. Bacterial species which constitute normal body flora (*Streptococcus viridans, Staphylococcus epidermidis* etc.) tend to cause a subacute illness due to their low invasiveness; they typically infect valves with preexisting abnormalities. Infections due to these organisms tend to be chronic and the average incubation period may be upto two weeks. These organisms gain entry into the bloodstream during dental, genitourinary or gastrointestinal procedures. The incidence of bacteremia after tonsillectomy is about 30%, after bronchoscopy it is 15% and after upper gastrointestinal endoscopy it is about 10%. The incidence of transient bacteremia after sigmoidoscopy is about 30% while instrumentation of the genitourinary tract it is as high as 60%. More virulent organisms (such as *Staphylococcus aureus, Streptococcus pyogenes, pneumococcus* or *gonococcus*) often infect healthy cardiac valves and the illness has a more fulminant course. Fungi (such as Candida species) often infect natural valves in intravenous drug abusers and in patients with prosthetic valves.

Pathogenesis Bacterial endocarditis occurs especially under conditions when the following three conditions exist: a) a high pressure jet from one cardiac chamber into another; b) a pressure gradient between the two chambers to provide the driving force for the jet; and c) a narrow orifice separating the two chambers. This explains why infective endocarditis is more common in patients with small intracardiac septal defects compared to those with large defects. The high velocity bloodstream impinges on the endothelium of cardiac valves and forms a sterile platelet-fibrin thrombus at the site of impact. This fibrin thrombus serves as a nidus for adhesion and multiplication of microorganisms; the fibrin covers the organisms providing them with protection from host defense mechanisms such as neutrophils, immunoglobulins and complement. The microorganisms destroy the valve tissue progressively. The infective vegetations increase in size and tend to dislodge and embolise into the blood stream ; they can block vascular supply to various organs and cause ischemia of the organ or tissue. Infective endocarditis involves the left-sided cardiac valves more often than the right-sided valves; the mitral, aortic, tricuspid and pulmonary valves are involved in descending order of frequency. Immune complexes are formed in infective endocarditis and these circulate and deposit within visceral capillaries; deposition on the wall of vessels can result in vasculitic phenomena, and in some cases aneurysm formation (mycotic aneurysm in the cerebral arteries).

Rheumatic valvular heart disease, congenital heart disease (ventricular septal defects and patent ductus arteriosus), mitral valve prolapse, and prosthetic valves are important predisposing causes. Right-sided endocarditis typically occurs in patients who abuse drugs or who have intravenous lines for a prolonged duration.

Infections of prosthetic valves or with virulent organisms are often associated with the formation of valve ring abscesses, myocardial abscesses and septic emboli. Without treatment, infective endocarditis is progressive and fatal. If treated with appropriate antimicrobials, the valve lesions heal by the endothelialisation of vegetations.

Clinical features The symptoms of the *subacute* form of the disease are often subtle and non-specific. Fever is an important symptom but its magnitude and pattern may vary

considerably. Infective endocarditis must be considered, therefore, in the differential diagnosis of any patient with pyrexia of unknown origin (PUO). Nonetheless, it must be remembered that fever may be absent in the elderly, and in those with renal failure or congestive heart failure. Chills, malaise, fatigue, anorexia (with weight loss) and arthralgia are frequently present. A history of dental work or genitourinary instrumentation may be an important clinical clue. Low back pain has been described as a presenting feature in upto a third of cases. Embolisation of various organs is a cardinal feature of infective endocarditis and results in a variety of manifestations depending on the site of embolism; left upper quadrant pain (spleen), chest pain (coronary arteries), hematuria (renal) and a spectrum of neurologic symptoms (hemiplegia, neuropsychiatric symptoms) can result. Embolisation to the large arteries of the extremities is uncommon with bacterial endocarditis but is frequent with fungal endocarditis. Symptoms of heart failure may develop and depend on the severity of the underlying valve lesion and the extent of valve destruction. *Acute* bacterial endocarditis usually presents as high grade fever with shaking chills; acute heart failure is frequently present as well.

Fever, anemia and a heart murmur are the cardinal clinical signs of subacute bacterial endocarditis. Certain peripheral signs of infective endocarditis have been noted and may be of diagnostic importance in the subacute form of the disease. Anemia is an important clinical sign, although alternative explanations such as a nutritional origin must also be kept in mind in developing countries. Clubbing of fingers in a patient with fever and a heart murmur should raise suspicion of endocarditis (in the absence of an alternative explanation such as cyanotic congenital heart disease). The finger nails may reveal *splinter hemorrhages* (15%); these are linear black-brown streaks located in the distal third of the nailbed.[1] Petechiae are also seen in 20–40 per cent of patients; these are red, non-blanching lesions which appear in crops on conjunctival, buccal or palatal mucosa and in the extremities. *Osler's nodes* (seen in 10–25%) are reddish-purple, tender nodules 1–10 mm in size, which appear on the pads of fingers or toes. *Janeway's lesions* are painless, macular, red or hemorrhagic patches which appear on the palms and soles (<10%). Fundoscopic examination is an important component in the examination of a patient with suspected endocarditis. *Roth's spots* are single or multiple, oval to fusiform retinal hemorrhages located near the optic disc and have a pale or white centre. Osler's nodes and Roth's spots are probably related to vasculitis, whereas Janeway's lesions are probably embolic in origin. Splinter hemorrhages and petechiae may be related either to vasculitis or to embolism. Spleno-megaly is an important sign and is present in 20 to 60 per cent of endocarditis patients with a subacute course of disease.

The most important clue to the diagnosis of endocarditis is the presence of a cardiac murmur (in 90 per cent). Changing cardiac murmurs (5–10%) or new cardiac murmurs (5%) are more specific but less frequent signs. A cardiac murmur may be absent very early in the phase of endocarditis, in patients with right-sided endocarditis and in patients with infective endarteritis or infection of an intravascular foreign object (such as an indwelling intravenous line). Signs of congestive heart failure are present in upto two-thirds of patients with endocarditis. Right-sided endocarditis is encountered in patients with a history of intravenous drug abuse, in subjects with indwelling intravenous lines, and in patients with congenital cardiac defects. The manifestations of right-sided endocarditis include fever, pleuritis, hemoptysis, the murmur of tricuspid regurgitation and septic pulmonary infarcts (appearing as multiple pulmonary shadows on the chest X-ray).

[1] This is a non-specific sign; these hemorrhages are present in labourers (related to trauma) and some patients with mitral stenosis in the absence of endocarditis.

Investigations Non-specific laboratory abnormalities are common in endocarditis and are often a function of the chronicity of the infection. The ESR is usually elevated. Leucocytosis is a feature of acute endocarditis. The leucocyte count may be normal in subacute endocarditis and there is usually an associated normocytic, normochromic anemia. The serum levels of globulins may be elevated and the rheumatoid factor may be positive. Urinalysis shows proteinuria (50%) and microscopic hematuria (30–50%), with the latter finding being relatively more specific. The ECG and chest X-ray findings are non-diagnostic and reflect the severity of the underlying cardiac disease. The ECG should be monitored for development of conduction blocks that may signify valve ring abscess formation in aortic valve endocarditis. Pulmonary infiltrates are common in right-sided endocarditis.

Blood cultures are one of the most important investigations in a patient with suspected endocarditis. A minimum of three sets of blood cultures should be obtained in the first 24 hours of hospitalisation. Additional blood cultures are important if the patient has received antibiotics in the preceding 2–3 weeks, and if the initial sets of culture are negative at 48–72 hours; these additional blood cultures should include cultures for fungi and anerobes. In developed countries, an organism can be isolated in up to 90 per cent of cases. In India, fewer than 50 per cent of the patients have positive blood cultures; improper collection techniques are likely to be an important factor. Some organisms (such as anerobes, Legionella, fungi) require specialised blood culture media. Other organisms such as Coxiella and chlamydial species require serologic tests for diagnosis.

Echocardiography is also an essential investigation in a patient with suspected endocarditis. Valvular vegetations can be detected in 60–80 per cent by the transthoracic approach and in over 90 per cent by the transesophageal approach (TEE). If possible, a TEE should be obtained in aortic valve endocarditis for better detection of valve ring abscesses, and in prosthetic valve endocarditis for better visualisation of vegetation. Echocardiography is also useful for monitoring the progress of vegetations in response to antimicrobial treatment and for assessing the extent of valvular and perivalvular damage.

Management Successful medical treatment requires the institution of therapy with an appropriate antimicrobial agent (based on blood cultures), maintaining high levels of the agents for an adequate length of time (usually 4–6 weeks), and monitoring the patient for treatment failure or for the development of complications.

Antibiotic treatment should be started empirically while awaiting blood culture reports. The common therapeutic regimens are listed in Table 12.28. Surgery in a patient with endocarditis is a matter of good clinical judgement. Usually a minimum of 24–72 hours of antibiotic trreatment is recommended prior to surgical intervention. Surgery (valve replacement) may be required under certain conditions: 1) severe congestive heart failure refractory to medical management; 2) failure of medical therapy; 3) development of complications such as valve ring abscesses or purulent pericarditis; 4) recurrent systemic emboli; and 5) endocarditis with unusual organisms (fungi). In patients with prosthetic valve endocarditis, the threshold for surgical treatment is lower as response to medical treatment alone is often unsatisfactory.

Prognosis Factors indicating a relatively adverse prognosis in infective endocarditis include old age, an acute onset of illness (as opposed to a subacute onset), left-sided endocarditis (as opposed to right-sided endocarditis), involvement of more than two valves, large size of vegetations, presence of a perivalvular abscess and a history of an embolic episode during the course of the illness.

Prophylaxis Infective endocarditis is a preventable disease. The avoidance of intravenous drug abuse and meticulous attention to dental hygiene are important measures. In persons with prior underlying heart disease, the precautionary use of antibiotics before procedures with a potential for bacteremia is advisable. The diseases where such prophylaxis is recommended and the common regimens used are listed in Table 12.29.

Prosthetic cardiac valves

Prosthetic cardiac valves may be *mechanical* or *bioprosthetic.* Mechanical valves are made of pyrolytic carbon or a metallic alloy and can be either of 'ball and cage' design (such as Starr-Edwards valve), or 'tilting disc' design (such as Bjork-Shiley valve, St. Jude valve). Mechanical valves require lifelong oral anticoagulation because of a high thrombogenicity but are sturdy and durable. Bioprosthetic valves are made from porcine valve tissue mounted on metal struts. These valves usually do not require anti-coagulation but are quite prone to structural degeneration.

All prosthetic valves are intrinsically stenotic and have small, clinically insignificant, residual transvalvular gradients. They are prone to infection. There is no prosthetic valve which is as good as the natural valve that a person is born with.

Cardiac tumours

Secondary tumours of the heart are more common than primary ones. Cardiac metastases are usually secondary to a thoracic tumour (breast and lung cancer being the commonest), a lymphoma or a malignant melanoma. Cardiac secondaries affect the pericardium more than the myocardium; endocardial metastases are unusual as the endocardium is avascular. Myocardial secondaries are most often clinically silent although conduction abnormalities have been described. Pericardial secondaries manifest as effusions or tamponade.

Primary tumours of the heart are often benign (75%) and myxomas are the commonest variety. Left atrial myxomas are 3 to 4 times more common than right atrial ones. Myxomas are occasionally familial, when they may also be multiple.

Left atrial myxomas are typically pedunculated structures arising from the fossa ovalis region. They are mobile and can obstruct the mitral orifice. The symptoms are similar to mitral stenosis with the exception that syncope is common in myxomas but very unusual in mitral stenosis. Myxomas often present with systemic features such as fever, arthralgia and weight loss. Myxomas may also present with embolic episodes due to detached tumour fragments. In left atrial myxomas, the clinical findings may mimic mitral stenosis but the murmur may vary with posture. A '*tumour plop*' may be heard in diastole; this sound is related to the striking of the atrial wall by the tumour when its movement is halted. The tumour plop occurs later than the opening snap and is lower in frequency. It occurs earlier than, and is higher in frequency than an S_3. An echocardiogram is diagnostic. Surgical excision is the treatment of choice but myxomas are known to recur (especially if the stalk is incompletely excised).

Table 12.28 Antibiotic treatment of infective endocarditis

Clinical situation/Organism	*Primary regimen*	*Alternative regimen*	*Duration/Comment*
Native valve endocarditis, while awaiting culture results			
Patient stable	Penicillin G 20 million U/day (divided doses q 4 h) + Gentamicin 1 mg/kg i.v. q 8 h	Vancomycin 15 mg/kg i.v. q 12 h + Gentamicin 1 mg/kg i.v. q 8 h	till culture results obtained; if culture results are negative and clinical response is favourable, continue for 4–6 weeks
Patient toxic, sick	Above + add penicillinase-resistant penicillin (Cloxacillin 2 g i.v. q 4 h)	above + consider adding imipenem if available	as above
Native valve endocarditis, culture positive			
Strep. viridans	Penicillin G 20 million U/day + Gentamicin 1 mg/kg i.v. q 8 h	Ceftriaxone 2.0 g i.v. q 12 h or Cefazolin 2 g i.v. q 8 h or Vancomycin 15 mg/kg i.v. q 12 h + Gentamicin 1 mg/kg i.v. q 8 h	4 weeks;gentamicin may not be required if penicillin G MIC≤ 0.1 μg/ml; streptomycin 7.5 mg/kg i.m. bd is an alternative to gentamicin
Enterococci	Penicillin G 20 million U/day or Ampicillin 2–4 g i.v. q 4 h + Gentamicin 1 mg/kg i.v. q 8 h	Vancomycin 15 mg/kg i.v. q 12 h + Gentamicin 1 mg/kg i.v. q 8 h	4–6 weeks
Staph. aureus	Penicillinase-resistant penicillin (Cloxacillin 2 g i.v. q 4 h) + Gentamicin 1 mg/kg i.v. q 8 h	Cefazolin 2 g i.v. q 8 h or Vancomycin 15 mg/kg i.v. q 12 h + Gentamicin 1 mg/kg i.v. q 8 h	4–6 weeks

Table 12.28 Antibiotic treatment of infective endocarditis (contd.)

Clinical situation/Organism	*Primary regimen*	*Alternative regimen*	*Duration/Comment*
Staph. epidermidis	Penicillinase-resistant penicillin (Cloxacillin 2 g i.v. q 4 h)	Cefazolin 2 g i.v. q 8 h or Vancomycin 15 mg/kg i.v. q 12 h	4–6 weeks
Prosthetic valve endocarditis			
Early (<2 months postoperative)	Vancomycin 15 mg/kg i.v. q 12 h + Gentamicin 1 mg/kg i.v. q 8 h + Rifampicin 300 mg q 8 h	Penicillinase-resistant penicillin (Cloxacillin 2 g i.v. q 4 h) + third generation cephalosporin + Gentamicin 1 mg/kg. i.v. q 8 h	6 weeks
Late (>2 months postoperative)	Penicillinase-resistant penicillin (Cloxacillin 2 g i.v. q 4 h) + Gentamicin 1 mg/kg i.v. q 8 h + Rifampicin 300 mg q 8 h	Vancomycin 15 mg/kg i.v. q 12 h + Gentamicin 1 mg/kg i.v. q 8 h + Rifampicin 300 mg q 8 h	6 weeks
Candida	Amphotericin B (i.v. 0.6 mg/kg/day for 7 days, then, 0.8 mg/kg every other day) + Flucytosine (100–150 mg/kg/day oral qid)		6–8 weeks; surgery may be required

MIC = minimum inhibitory concentration

Table 12.29 Antimicrobial prophylaxis for prevention of bacterial endocarditis

Clinical consideration	*Prophylaxis recommended*	*Prophylaxis not recommended*
Cardiac conditions	prosthetic valves, prior episode of endocarditis, most congenital heart diseases (other than secundum atrial septal defect), hypertrophic cardiomyopathy, mitral valve prolapse with valve regurgitation	previous coronary artery bypass surgery, mitral valve prolapse without valve regurgitation, innocent murmurs, isolated secundum atrial septal defect, cardiac pacemakers
Surgical procedures	dental procedures, tonsillectomy, surgical procedures on the gastrointestinal or urinary tract (sclerotherapy, colonoscopy, urethrocystoscopy), drainage of infected abscesses	endotracheal intubation, fibreoptic bronchoscopy, cardiac catheterisation, urethral catheterisation, uncomplicated vaginal delivery

Site of procedure	*Standard regimen*		*Alternative regimen*		
	Drug	*Dose (adults)*	*Reason*	*Drug*	*Dose (adults)*
Dental, oral, upper respiratory tract	Amoxicillin	3.0 g orally 1 hour before procedure, then 1.5 g oral 6 hours later	Unable to take oral medication	Ampicillin	2.0 g i.v. 30 mins before,1.0 g i.v. 6 hours after procedure
			Penicillin allergy	Erythromycin	1.0 g oral 2 hours prior, 500 mg 6 hours after procedure
				Vancomycin	1.0 g i.v. over 1 hour, starting 1 hour before procedure
Genitourinary/ gastrointestinal procedures	Ampicillin + gentamicin, followed by amoxycillin	Ampicillin 2 g i.v. + gentamicin 1.5 mg/kg i.v. 30 mins before, amoxicillin 1.5 g oral 6 hours after procedure	Penicillin allergy	Vancomycin+ Gentamicin	Vancomycin 1 g i.v. (over 1 hour)+ gentamicin 1.5 mg/kg i.v. 1 hour before procedure

KEY CONCEPTS

Rheumatic fever

- RF is an acute non-suppurative complication of Group A streptococcal pharyngitis that affects children 5–15 years of age. RF increases with conditions leading to overcrowding.
- The histologic hallmark of RF is the Aschoff nodule in the myocardium, the synovium and other involved tissues (subcutaneous nodules).
- Polyarthritis is the most common manifestation. It tends to affect the large joints and typically has a migratory pattern.
- The carditis of RF is a pancarditis characterised by myocarditis (usually without affecting systolic function), valvulitis (murmurs, mitral regurgitation being the most common) and pericarditis (pericardial friction rub). Cardiac enlargement and heart failure in RF are usually the result of hemodynamically significant valvulitis.
- Subcutaneous nodules (over the extensor surfaces of bones) and chorea (Sydenham's chorea) are late manifestations of RF. Erythema marginatum is a transitory skin rash characteristic of RF which is rare in dark skinned individuals.
- A diagnosis of RF is considered when Jones criteria for diagnosis are met: the presence of 2 major criteria (carditis, polyarthritis, chorea, subcutaneous nodules and erythema marginatum) or of 1 major and 2 minor criteria (fever, arthralgia, previous history of RF, and evidence of acute phase reactants). The clinician must also seek objective evidence of recent streptococcal infection (essential criteria: ASLO, throat swab).
- Recurrences of RF tend to be mimetic. The most important sequelae of RF is related to valvulitis with consequent chronic valvular destruction.
- The treatment includes bedrest, penicillin (for eradicating streptococci in the throat), and aspirin/steroids (the latter being preferred in the presence of CHF). Penicillin prophylaxis (1.2 million units benzathine penicillin i.m every 21 days) is recommended for at least five years after the index attack (and preferably till adulthood).

Mitral stenosis

- MS is nearly always the result of rheumatic fever (though no history of RF may be forthcoming in 50%); RF results in fusion of valve commissures and fibrosis of subvalvular apparatus.
- The normal mitral valve area (MVA) is 4–6 cm^2; an MVA <2 cm^2 is regarded as hemodynamically significant, while an MVA <1 cm^2 indicates severe MS.
- MS impedes LV filling causing increased LA pressure which is passively transmitted to the pulmonary veins. Reactive pulmonary arterial vasoconstriction further aggravates pulmonary hypertension. Increased PA pressure results in a decreased forward cardiac output and imposes an increased afterload on the RV. Increased LA pressure results in dyspnea, othopnea and episodes of paroxysmal nocturnal dyspnea. RV failure results in systemic venous congestion (with peripheral edema, hepatic congestion, ascites, and anorexia). The other important manifestations are hemoptysis, systemic embolism (in the presence of atrial fibrillation) and hoarseness of voice.
- Physical examination reveals a small volume pulse, a tapping apical impluse, a parasternal lift, a loud S_1, increased intensity of P_2 , an opening snap (OS) following S_2 (in cases with a pliable valve), and a mid-diastolic rumble at the apex with presystolic accentuation. A long diastolic murmur and a short A_2-OS interval indicate severe MS.
- The ECG shows left atrial overload (P mitrale; peaked notched P waves), and RVH; atrial fibrillation may be present. In patients with severe MS the chest X-ray reveals LA appendage enlargement, prominent PA segment (straight left heart border), LA enlargement (double contour) and Kerley B lines.
- The echocardiogram is helpful in assessing the severity of MS (AV pressure half-time, 2-D planimetry) and the mobility and thickness of valve leaflets (which determines suitability for MV balloon dilatation). In patients with pure MS, cardiac catheterisation is indicated only if there is a suspicion of coronary disease or additional rheumatic involvement of other valves.
- The medical treatment of severe MS includes judicious use of diuretics, digitalis and anticoagulants. In patients with atrial fibrillation, beta-blockers and the calcium channel blockers (verapamil, diltiazem) represent alternatives/adjuncts to digitalis for controlling rapid ventricular response.
- The treatment options for severe MS with pliable valve leaflets and without major subvalvular deformity include balloon dilatation, and closed/open mitral commissurotomy. If the mitral valve is calcific, deformed and associated with severe degree of subvalvular deformity or significant mitral regurgitation, mitral valve replacement is the preferred mode of treatment. All patients should receive prophylaxis against rheumatic recurrences and bacterial endocarditis.

Mitral regurgitation

- MR may be chronic (RHD, MVP, cardiomyopathy, immunoinflammatory disease) or acute (infective endocarditis with perforation of valve leaflet, papillary muscle rupture following MI, rupture of chordae tendineae).
- Mild MR is usually asymptomatic. When the valve lesion is moderate to severe in severity, exertional dyspnea, fatigue and orthopnea emerge as important symptoms. Acute MR usually presents with sudden, severe CHF and cardiovascular collapse.
- The clinical features in chronic severe MR include cardiomegaly, wide variable split S_2, S_3, pansystolic murmur at the apex (radiating to the axilla) and apical diastolic flow rumble. The murmur in MVP may be late systolic and preceded by a click. The murmur of papillary muscle dysfunction is crescendo (to S_2) in character. In acute MR there is a decrescendo systolic murmur; the murmur radiates to the carotids when the posterior chordae are ruptured whereas it radiates to the spine when there is rupture of anterior chordae.
- The ECG shows LA and LV volume overload. The chest X-ray shows enlarged LA and LV and pulmonary venous hypertension of varying degrees.
- Doppler echocardiography is diagnostic; it quantitates the degree of MR, identifies potential mechanisms and assesses LV size.
- The treatment consists of endocarditis prophylaxis and medical measures targeted to the degree of MR, patient's symptoms and LV function. Mild to moderate MR can be managed with dietary salt restriction, and afterload reducing agents (vasodilators). If MR is severe, diuretics, digoxin may be additionally required. Surgery is contemplated when the LVIDes exceeds 45 mm. Acute MR requires initial stabilisation followed often by immediate surgery. Surgical options for patients with MR include annuloplasty, valve repair and valve replacement.

Aortic stenosis

- The normal aortic valve area (AVA) is 2–3 cm^2 ; an AVA <1 cm^2 indicates significant aortic stenosis.
- The common causes of AS include congenital bicuspid aortic valve, degenerative calcific AS (senile), and rheumatic valvular heart disease (usually with coexistent mitral valve disease). Irrespective of the cause, AS imposes a pressure overload on the left ventricle; this results in concentric LVH.
- The cardinal symptoms of AS include angina, exertional syncope (due to a failure of cardiac output to increase in the face of a fall in peripheral resistance) and dyspnea. CHF is a feature of severe AS.
- The clinical findings include pulsus parvus et tardus, systolic thrill at the base of the heart, a sustained LV type of apex, normal S_1, soft A_2, S_4, and S_3 (when there is CHF), and late peaking ejection systolic murmur in the aortic area which radiates to the carotids.
- The ECG shows LVH. Chest X-ray features include calcification of the aortic valve (the absence of calcification in an adult suggests that the AS is not severe), poststenotic dilatation of the aorta, and cardiomegaly with an LV contour of the apex. The echocardiogram is diagnostic and Doppler yields a transvalvular gradient and the AVA. Cardiac catheterisation is required in adults over 45 years of age, principally to exclude coexistent coronary artery disease.
- The treatment consists of endocarditis prophylaxis, avoidance of strenuous exercise and relief of valvular stenosis (for moderate to severe AS); balloon valvotomy may be used in children with a bicuspid aortic valve with severe stenosis, while valve replacement is preferred in adults with valvular aortic stenosis.

Aortic regurgitation

- AR may be chronic (*valve disease*: rheumatic disease, bicuspid aortic valve; *root disease*: Marfan syndrome, ankylosing spondylitis, syphilis) or acute (endocarditis, aortic dissection, and prosthetic valve dehiscence).
- Irrespective of the cause, AR results in chronic LV volume overload, eccentric LV hypertrophy, increase in stroke volume, and lowering of the diastolic blood pressure (resulting in a widened pulse pressure).
- The symptoms of chronic AR include palpitations (especially prominent on recumbency), exertional dyspnea, sweating, and angina (in 5% tends to be nocturnal when the slow heart rate increases degree of AR). Acute AR results in acute pulmonary edema and cardiovascular collapse.
- The clinicial findings on physical examination include a bisferiens pulse, wide pulse pressure with prominent arterial pulsations, forceful hyperdynamic apical impluse, basal diastolic thrill, an S_3 and the typical high pitched decrescendo early diastolic murmur along the left sternal edge (more prominent on leaning forward and in expiration). There may be a low pitched apical diastolic rumble (Austin Flint murmur, related probably to the AR jet impinging on the anterior mitral leaflet) and a systolic flow murmur across the aortic valve.
- The ECG shows LV volume overload while the chest X-ray reveals cardiomegaly with a dilated ascending aorta. Doppler echocardiography is diagnostic and

helps to determine the etiology (root vs valve disease), to quantify the degree of regurgitation and to assess its impact on the LV function.

➢ Asymptomatic patients with AR may benefit from treatment with vasodilators, require digoxin and diuretics; definitive treatment consists of valve replacement which is considered when the LVIDes exceeds 55 mm. Emergency surgery may be required for acute onset AR. Endocarditis prophylaxis is standard practice.

Infective endocarditis

➢ IE is the infection of previously deformed cardic valves (rheumatic valve disease, MVP, bicuspid aortic valve; *viridans streptococci* is most often the agent), normal cardiac valves (usually associated with i.v. drug abuse; staphylococcus aureus is the most common causative organism), prosthetic valves (staphylococci are the most frequent agent for *early* infections [<2 months after cardiac surgery]; streptococci are responsible for most *late* infections [>2 months after surgery]), non-valvular endocardium (often the area of the jet lesions in shunts, e.g. VSD) and vascular endothelium (endarteritis as in PDA).

➢ Transient bacteremia during dental procedures, or due to genitourinary or gastrointestinal instrumentation is often the initiating event.

➢ The cardinal feature of IE is the presence of fever in a patient with a cardiac murmur. Additional symptoms include malaise, lethargy, weight loss, anorexia or a major embolic episode. The supportive findings on physical examination include anemia, clubbing, splenomegaly, Roth's spots in the retina, Osler's nodes and Janeway's lesions. Right-sided endocarditis presents with multiple pulmonary infarcts, hemoptysis, pulmonary infiltrates, and right heart failure (in the setting of a predisposing cause like i.v. drug abuse or the use of central venous lines).

➢ Potential complications include CHF, formation of valve root abscesses with extension into adjacent structures, leaflet perforation and valve dehiscence (in the case of prostheses), systemic embolism and metastatic abscesses.

➢ Obtaining multiple blood cultures prior to initiating antibiotic therapy is critical; successive cultures over a 24–36 hour period (often plated on specialised media) increase the diagnostic yield. Urinalysis may reveal microscopic hematuria. Echocardiography is the investigation of choice and vegetations are the hallmark of IE (demonstrated in 60–80% by transthoracic echo). TEE increases diagnostic yield (over 90%) and is especially recommended for aortic valve endocarditis (increases diagnosis of complications like valve root abscess) and for prosthetic valve endocarditis. Serial ECGs may help monitor complications like root abscesses.

➢ The treatment consists of parenteral administration of high microbicidal doses of the appropriate antibiotic for a prolonged period (for native valve endocarditis). Prosthetic valve endocarditis frequently necessitates valve replacement in addition to medical management. Surgery should also be considered for fungal endocarditis, mechanical complications (like CHF, valve dehiscence), root abscess formation or multiple embolic episodes.

➢ Prevention is possible by meticulous attention to antibiotic prophylaxis in patients with valve disease.

12.9 Myocardial disease

MYOCARDITIS

Myocarditis is said to be present when the the heart is involved in an inflammatory process. The inflammation involves the myocytes, the interstitium, the vascular elements and/or the pericardium. When pericardial inflammation is present alongwith myocardial inflammation, the term *myopericarditis* is often used. The diagnostic criteria for myocarditis include demonstration of myocyte necrosis or myocytolysis, in the presence of an inflammatory myocardial infiltrate.

Etiology Myocarditis is most often the result of an infectious process. It may however sometimes be due to a hypersensitivity state such as acute rheumatic fever, or may be caused by radiation, chemicals, physical agents or drugs. Infectious myocarditis may be due to viral agents, bacteria, fungi or protozoal infection. The most common cause of myocarditis is infection due to viruses. Coxsackie B virus is the most frequent cause of viral myocarditis but other viruses like Coxsackie A virus, adenoviruses, echoviruses and influenza may also cause the disease. Bacterial myocarditis is uncommon and is usually a complication of bacterial endocarditis especially by agents such as *Staphylococcus aureus*. Diphtheria is complicated by myocarditis in upto a quarter of patients. Protozoans which involve the myocardium include *Toxoplasma gondii* and *Trypanosoma cruzi*, the latter causing *Chagas' disease*.

Pathology The histological criteria for the diagnosis of myocarditis have been mentioned above. In acute myocarditis the hearts are flabby and show focal hemorrhages. On microscopic examination, the inflammatory infiltrate may be composed of a variety of cell types depending on the underlying etiology. Thus, in viral myocarditis lymphocytes predominate, in bacterial myocarditis polymorphonuclear cells predominate and in hypersensitivity myocarditis eosinophils are seen in abundance. The hallmark of rheumatic myocarditis is the Aschoff-nodule (see section 12.8). Giant cells are common in sarcoid-related myocarditis.

Clinical manifestations Myocarditis is associated with non-specific clinical symptoms which include fatigue, dyspnea, palpitations and chest pain. Chest pain usually reflects associated pericarditis (myopericarditis). In viral myocarditis there may or may not be a history of a preceding viral illness. This includes a history of a preceding upper respiratory tract illness or nasopharyngitis or tonsillitis. Diphtheritic myocarditis usually occurs after the first week of illness. Occasionally, there may be evidence of fulminant congestive heart failure occurring over a short period.

The physical examination may be normal in patients with mild myocarditis but may reveal a muffled first heart sound, a prominent third heart sound and occasionally, a pericardial friction rub. Tachyardia is usual and in florid

cases there may be clinical evidence of congestive heart failure.

Investigations The ECG is usually abnormal, the most common changes being abnormalities of the ST segment and the T wave.

Atrial and ventricular arrhythmias, and atrioventricular and intraventricular conduction defects may be seen. The chest X-ray may or may not reveal cardiac enlargement. The echocardiogram is often useful in demonstrating some degree of left ventricular dysfunction. Radionuclide scanning with indium-111 labelled antimyosin antibody may identify the inflammatory myonecrosis characteristic of myocarditis but it is available at few centres in India. The diagnosis of viral myocarditis is supported by the identification of the virus in stool specimens and throat washings or by demonstrating a distinct rise in antibody titres. However, cultures are usually negative and serological tests are non-diagnostic. Endomyocardial biospy is therefore frequently used to confirm the diagnosis of myocarditis. It however, does not yield an etiologic diagnosis of the illness.

Natural history Viral myocarditis is most often self-limited and without sequelae. Occasionally acute myocarditis progresses to a chronic form and leads to dilated cardiomyopathy. Deaths have been attributed to heart failure, tachyarrhythmias and heart block.

Management Therapy for acute myocarditis is often supported and directed at the more prominent systemic manifestations of the disease. Prolonged bedrest has been advocated for severe myocarditis. Patients who develop congestive heart failure respond to the usual measures of diuretics, digitalis and salt restriction but they may be unusually sensitive to digitalis.

Corticosteroids and immunosuppressive agents have not been shown to be of benefit in patients with idiopathic myocarditis.

CARDIOMYOPATHY

The cardiomyopathies are a heterogeneous group of disorders which primarily affect the heart muscle. They are thus distinguished from other recognisable processes which may affect the myocardium such as coronary artery disease, hypertension, valvular heart disease and congenital heart disease. In the stricter sense, cardiomyopathies are defined as '*heart muscle diseases of unknown etiology*'. However, this definition, which automatically excludes conditions in which there is a specific pathologic process causing the myocardial disease, is not accepted by all and terms such as alcoholic ischemic cardiomyopathy are frequently used. There is a general agreement on a functional classification of cardiomyopathies into three categories based on clinical, hemodynamic and structural features : 1) dilated cardiomyopathy; 2) hypertrophic cardiomyopathy; 3) restrictive cardiomyopathy. A comparison of the important features of the three common forms of cardiomyopathy is shown in Table 12.30.

Idiopathic Dilated Cardiomyopathy

Dilated cardiomyopathy is a syndrome characterised by dilatation of one or both ventricles and impaired systolic function of either ventricles.

Etiology and pathology In its strictest use, dilated cardiomyopathy is a disease where a known etiology of heart failure cannot be recognised. However, several diseases of heart muscle may produce clinical manifestations similar to a dilated cardiomyopathy and this common use has eroded the strictest use of the term dilated cardiomyopathy. At least four conditions have been recognised as appearing to lower the threshold for the development of cardiomyopathy. These include chronic excessive ingestion of alcohol, pregnancy and the postpartum state, systemic hypertension, and a variety of viral illnesses. Other less common

Table 12.30 Comparison of three types of cardiomyopathies

Feature	*Dilated*	*Restrictive*	*Hypertrophic*
Symptoms	• Dyspnea, fatigue • Right-sided CHF • Systemic or pulmonary emboli	• Dyspnea, fatigue • Right-sided CHF • Chest pain, angina • Symptoms/signs of systemic disease (amyloid, iron storage disease)	• Dyspnea, fatigue • Chest pain, angina • Syncope, sudden death, palpitations
Physical examination	• Moderate-severe cardiomegaly • S_3 • Atrioventricular valve regurgitation	• Mild cardiomegaly • S_3/S_4 • Atrioventricular valve regurgitation • Inspiratory increase in jugular venous pressure (Kussmaul's sign)	• Apical systolic thrill, heave • Bisferiens pulse, brisk carotid upstroke • S_4 • Systolic murmur that increases with Valsalva maneuver
Chest X-ray	• Moderate-severe cardiomegaly • Pulmonary venous hypertension • Left atrial enlargement	• Mild-moderate cardiomegaly • Pulmonary venous hypertension • Left atrial enlargement	• Normal heart size–mild cardiomegaly • Left atrial enlargement
ECG	• Atrial and ventricular arrhythmias • ST-T changes • Intraventricular conduction defects	• Low voltage • Atrial enlargement • AV conduction disturbances	• Left ventricular hypertrophy • Abnormal Q waves • ST-T changes

Table 12.30 Comparison of three types of cardiomyopathies (contd.)

Feature	*Dilated*	*Restrictive*	*Hypertrophic*
Echo-cardiogram	• Left ventricular dilatation	• Biatrial enlargement	• Asymmetrical hypertrophy of septum relative to posterior wall (ASH)
	• Systolic ventricular dysfunction	• Small-normal left ventricular cavity	• Vigorous systolic ventricular function
	• Atrioventricular valve regurgitation	• Normal ventricular systolic function	• Systolic anterior motion (SAM) of mitral valve
		• AV valve regurgitation	• Doppler evidence of dynamic outflow tract gradient
		• Increased wall thickness,'sparkling' appearance (amyloid)	
		• Apical obliteration of ventricle, tethering of atrioventricular valves, dilated right ventricular outflow (EMF)	• Mitral regurgitation
Cardiac catheterisation	• Left ventricular enlargement and systolic dysfunction	• Normal left ventricular systolic function	• vigorus systolic function
	• Elevated filling pressures	• Elevated filling pressures	
		• Apical ventricular obliteration (EMF)	• Dynamic ventricular outflow tract gradient
		• 'Square root' sign in ventricular pressure recording	
Endomyocardial biopsy	• Non-specific in the absence of underlying inflammatory myocarditis	• May reveal infiltrative disease (amyloid, iron storage)	• Not indicated
			• May reveal cellular disarray

S_3, S_4, are third and fourth heart sounds, EMF= Endomyocardial fibrosis

causes that contribute to the development of a dilated cardiomyopathy include infection with human immunodeficiency virus, cocaine abuse, cardiotoxicity of a variety of anticancer drugs, especially adriamycin and 5 fluorouracil. A dilated type of cardiomyopathy has been recognised in patients with Duchenne's progressive muscular dystrophy.

Pathologically, there is enlargement and dilatation of all the four cardiac chambers, the ventricles being more dilated than the atria. The cardiac valves are intrinsically normal, and intracavitary thrombi, particularly in the ventricular apex, are common. Microscopic examination reveals extensive areas of interstitial and perivascular fibrosis.

Clinical features Dilated cardiomyopathy is more common in middle-aged men. However, no age or sex is exempt. Symptoms usually develop gradually over a period of months or years. The more striking symptoms are those related to left ventricular failure and they include fatigue, weakness, and a diminished exercise tolerance. Symptoms of right heart failure are generally late and are associated with a particularly poor prognosis. Although atypical chest pain may be present in these patients, the presence of typical angina pectoris is unusual and should suggest the presence of concomitant coronary artery disease. Symptoms related to systemic or pulmonary emboli are not uncommon in these patients and often complicate the natural history of dilated cardiomyopathy. Ventricular arrhythmias are frequent and a common cause of sudden death in these patients.

The physical examination usually reveals variable degrees of cardiac enlargement and findings of congestive heart failure. The apical impulse is usually displaced laterally due to left ventricular dilatation. The pulmonic component of the second heart sound may be accentuated due to pulmonary hypertension. Ventricular gallops (S_3) are the rule once cardiac decompensation occurs. Systolic murmurs of mitral or tricuspid regurgitation are common and are related to dilatation of the mitral and tricuspid anulus, respectively.

Investigations The electrocardiogram is frequently abnormal. The findings include sinus tachycardia, atrial and ventricular arrhythmias, intraventricular conduction defects and ST segment and T wave abnormalities. A poor progression of R waves over the right precordial leads is common. The chest X-ray reveals moderate to marked cardiac enlargement especially of the left ventricle (Fig 12.66). Pleural effusions may be present and the right-sided chambers may be enlarged when right heart failure supervenes. Two-dimensional echocardiography is useful in assessing the degree of impairment of the right and left ventricles, and for documenting regurgitation of right-sided or left-sided atrioventricular valves. It is also useful for detecting ventricular thrombi. Cardiac catheterisation and coronary arteriography are usually carried out to rule out concomitant or underlying coronary artery disease. Coronary arteriography usually reveals normal coronary vessels. Other findings on cardiac catheterisation include elevation of the right ventricular end-diastolic pressure, elevation of left atrial and pulmonary capillary wedge pressures.

Management Treatment of idiopathic dilated cardiomyopathy is the treatment of heart failure in this condition. Diuretics, digoxin and vasodilator therapy can be combined judiciously; vasodilators have been shown to prolong life in subjects with heart failure and dilated cardiomyopathy. Cautious use of gradually increasing doses of beta adrenoceptor blockers have been used in these patients and can result in a significant improvement in symptoms. The mechanism of action to beta-blockade seems to be multifactorial, that is, an increase in myocardial beta adrenoceptor density, a reduction of sympathetically-mediated vasoconstriction, and a negative chronotropic effect that reduces myocardial oxygen demand.

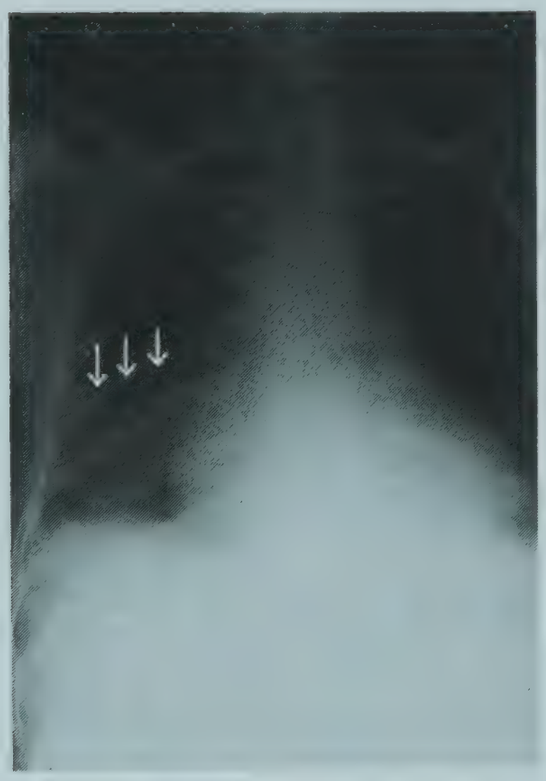


Fig 12.66 Plain X-ray chest (PA view) of a 49-year old man with progressive dyspnea. There is marked cardiac enlargement of the heart (LC, RA, LA). The horizontal fissure (multiple arrows) is thickened and upper lobe pulmonary veins prominent (antler sign) suggesting severe pulmonary hypertension. This patient had a dilated cardiomyopathy

Oral anticoagulants have been used in these patients routinely due to evidence that systemic and pulmonary emboli can cause considerable morbidity and mortality. Antiarrhythmic agents may be used to treat symptomatic serious arrhythmias. In patients with advanced cardiac failure which is refractory to medical therapy, cardiac transplantation is an alternative. It is, however, available only at a few centres. When alcohol intake is identified as an important underlying factor in dilated cardiomyopathy, immediate and total abstinence from alcohol intake is advisable and may improve ventricular function and patient survival.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a disorder characterised by inappropriate myocardial hypertrophy, often involving the interventricular septum of a non-dilated left ventricle, along with hyperdynamic ventricular systolic function and diastolic dysfunction related to the increased stiffness of the hypertrophied left ventricular myocardium. The disease appears to be genetically transmitted in roughly half the patients as an autosomal dominant trait with variable expression and penetrance. In some families the disorder may be caused by a genetic defect in a locus on the long arm of chromosome 14.

Pathology and pathophysiology On macroscopic examination, there is a marked increase in myocardial mass and the ventricular cavities are small. The left ventricle is usually more hypertrophied than the right, and both atria may be dilated reflecting the increased resistance to the filling of the ventricles. The pattern of ventricular hypertrophy is variable but in more than 90 per cent of patients, the hypertrophy is largely localised to the interventricular septum and the anterolateral wall of the left ventricle as compared with the posterior left ventricular free wall. The term *asymmetrical septal hypertrophy* is used in this context. A variant seen in parts of Asia involves hypertrophy of the apex of the left

ventricle predominantly (*apical hypertrophic cardiomyopathy*). The intramural coronary arteries are frequently abnormal in hypertrophic cardiomyopathy with a prominent reduction in the size of their lumen and thickening of their walls. The microscopic hallmark of hypertrophic cardiomyopathy is *myofibrillar disarray.* This refers to a gross and bizarre disorganisation of muscle bundles resulting in a characteristic whorled pattern. Abnormalities are found in the cell to cell arrangement as well as in the organisation of myofibrillar architecture within a myocyte.

The pathophysiologic hallmark of hypertrophic cardiomyopathy is diastolic dysfunction with or without left ventricular outflow tract obstruction. About 25–30 per cent of patients with hypertrophic cardiomyopathy demonstrate an outflow tract gradient whereas the diastolic dysfunction is ubiquitous in this disorder. The ventricular septal hypertrophy causes anatomic narrowing of the left ventricular outflow tract. The hyperdynamic left ventricular function results in blood being ejected rapidly through a narrowed outflow tract. This results in Venturi forces that draw the anterior mitral leaflet towards the septum. Mitral *leaflet-septal contact* results in obstruction to the left ventricular outflow tract and this anterior motion of the mitral leaflet results in improper coaptation of the mitral leaflet with consequent mitral regurgitation. This ventricular outflow tract obstruction is not fixed but is dynamic, that is, it varies depending on the size of the left ventricle, the size of the outflow tract and the force of ventricular ejection. Thus, conditions which increase the left ventricular contractility (such as infusion of inotropic agents), conditions which decrease the ventricular volume and thereby further decrease the size of the outflow tract (preload reducing maneuvers) all serve to increase the ventricular outflow tract obstruction. Therefore, this ventricular outflow tract obstruction tends to vary from one examination to another and occasionally even from beat to beat. It is this left ventricular outflow tract obstruction that causes the characteristic harsh, crescendo-decrescendo mid-systolic murmur and the associated mitral regurgitation that begins at the time of leaflet-septal contact. Diastolic dysfunction is universal in hypertrophic cardiomyopathy whether or not the outflow tract gradient is present. The hypertrophied ventricle is stiff and difficult to fill resulting in increased filling pressures in the atria. Both early diastolic filling as well as late diastolic filling are impaired in this disorder. Electrical instability is also typical of hypertrophic cardiomyopathy. Ventricular arrhythmias occur in over three-fourths of patients. Ventricular tachycardia is found in about 25 per cent of patients and in some it is a harbinger of sudden cardiac death. Myocardial ischemia is also an important feature of hypertrophic cardiomyopathy. It is multifactorial in etiology. It may be related to the narrowed, small, intramural coronary arteries, increased oxygen demand due to hypertrophied ventricles, and decreased coronary perfusion due to elevated filling pressures in the ventricles.

Clinical features The majority of patients with hypertrophic cardiomyopathy are asymptomatic or only mildly symptomatic. The disease is identified most often in adults in the third or fourth decade of life with a slight male predominance. Though general, the severity of symptoms varies directly with the extent of myocardial hypertrophy; this relation is not absolute. Some patients have severe symptoms with only mild myocardial hypertrophy and vice versa. The most common symptom is dyspnea largely due to increased ventricular filling pressure leading to elevated left atrial pressure and consequent elevated pulmonary venous pressure. Other clinical features include chest pain (often typical angina pectoris), fatigue, and syncope. Syncope may result from inadequate cardiac output with exertion (with an increase in the outflow tract gradient) or due to cardiac arrhythmias. The clinical presence of a history of

syncope or pre-syncope especially in young adolescents identifies patients who are at increased risk for sudden cardiac death.

The physical findings in a patient with hypertrophic cardiomyopathy are characteristic. The carotid pulse rises rapidly and typically has a double peak. This pulse pattern with two systolic peaks is called the *bisferiens pulse.* The initial peak called the *percussion wave* is due to the rapid rise of the pulse with initial rapid ventricular ejection. After that with the onset of outflow tract obstruction there is a sudden decrease in the rate of ventricular ejection and this is followed by a smaller and a more slowly rising systolic pulse wave, the *tidal wave.* Similarly, the apical impulse on palpation is displaced laterally and may be triphasic. The initial systolic impulse is followed by a second late systolic impulse as ventricular contraction resumes after the outflow tract obstruction subsides. A prominent presystolic apical impulse arises from forceful atrial systole as the atria force blood into the stiff hypertrophied ventricles. The auscultatory counterpart of this presystolic impulse is a prominent fourth heart sound. The auscultatory hallmark of hypertrophic cardiomyopathy with obstruction is a systolic murmur which is harsh, crescendo-decrescendo and is heard best between the lower left sternal border and the apex. The murmur begins after the first heart sound since early ejection in systole is unimpeded in hypertrophic cardiomyopathy. There may be another murmur which is holosystolic and blowing in character and more often heard at the apex and the axilla. This is a murmur of mitral regurgitation that usually accompanies obstructive hypertrophic cardiomyopathy.

The loudness of the systolic murmur is affected by factors which change the ventricular volume or ventricular contractility and thereby alter the severity of the outflow tract obstruction. A decrease in ventricular volume, an increase in ventricular contractility or a decrease in ventricular afterload all serve to increase the severity of obstruction and therefore decrease the intensity of the murmur in obstructive hypertrophic cardiomyopathy. Thus, the murmur of hypertrophic obstructive cardiomyopathy increases with the Valsalva maneuver or while standing (maneuvers that reduce ventricular volume), and with the administration of isoprotorenol or with exercise (maneuvers that increase myocardial contractility). The murmur decreases with squatting, hand grip, and the administration of phenylephrine (maneuvers that increase ventricular afterload).

Investigations The electrocardiogram commonly shows left ventricular hypertrophy and ST wave abnormalities. Abnormal Q waves which are broad and that could suggest an old myocardial infarction (*pseudoinfarction pattern*) may be found in upto 50 per cent of patients. There may be evidence of left atrial enlargement. The chest X-ray may be normal although mild increase in the diameter of the cardiac silhouette is common. The echocardiogram is the investigation of choice for the diagnosis of hypertrophic cardiomyopathy (Fig 12.67). The septum is typically more hypertrophied than the left ventricular posterior wall (being 1.3 or more times the thickness of the latter). There may be an abnormal increased echogenicity of the septum and septal excursion may be reduced on M-mode echocardiograms. Two-dimensional echocardiography reveals a small hypercontractile left ventricle and systolic anterior motion (SAM) of the anterior mitral leaflet, a feature classically described on the M-mode echocardiogram. The left ventricular outflow tract may be narrowed and there may be evidence of turbulence within the left ventricular cavity on colour flow Doppler imaging. A dynamic outflow tract gradient may be documented and measured by Doppler echocardiography and mitral regurgitation beginning typically at the time of leaflet-septal contact can be documented. Cardiac catheterisation is usually not necessary for the

diagnosis of hypertrophic cardiomyopathy. When performed, the typical hemodynamic features are an elevation in the left ventricular end-diastolic pressures which indicate diminished ventricular compliance, and when obstruction is present, a systolic pressure gradient between the body of the left ventricle and the subaortic region.

Natural history Only a minority of patients with hypertrophic cardiomyopathy are symptomatic. The natural history of hypertrophic cardiomyopathy does not correlate with the presence or the magnitude of outflow tract obstruction. There is an annual mortality of four per cent usually due to sudden cardiac death that tends to predominate in younger patients and in those with a family history of sudden cardiac death. Five to ten per cent of patients may have symptoms of congestive heart failure. A further 3–4 per cent may suffer from cerebrovascular accidents related to either decreased cerebral perfusions during episodes of syncope, or to emboli from ventricular thrombi or mitral valve vegetations. Infective endocarditis, atrial fibrillation, and systemic embolism may complicate the natural history of hypertrophic cardiomyopathy. The presence of ventricular tachycardia on ambulatory Holter monitoring is a predictor of sudden cardiac death.

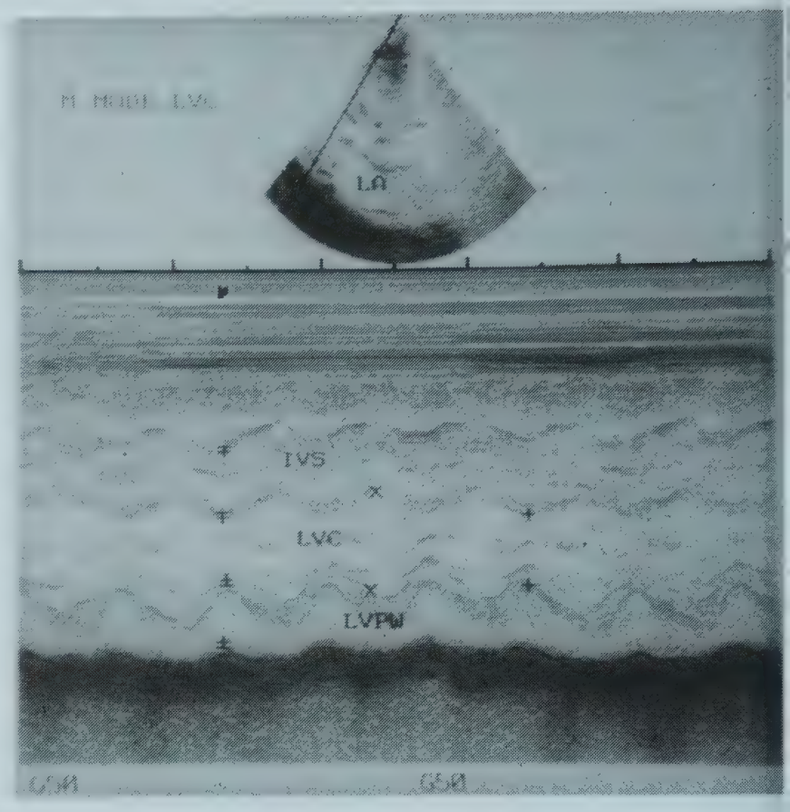


Fig 12.67 M-mode echocardiographic image in a subject with hypertrophic cardiomyopathy. Note the markedly hypertrophied and hypokinetic ventricular septum (IVS) as compared to the left ventricular posterior wall (LVPW).

Management Both beta-blockers and calcium channel blockers have been used in the treatment of hypertrophic cardiomyopathy. Beta-blockers are the drug of choice in symptomatic patients with outflow tract obstruction. Calcium channel blockers like verapamil may be used both in the presence and in the absence of outflow tract obstruction and serve to improve the ventricular compliance. Disopyramide has been used in some patients to reduce left ventricular contractility and thereby the outflow tract gradient. Antiarrhythmic drugs (particularly amiodarone) may be beneficial in the treatment of symptomatic atrial and ventricular tachyarrhythmias. Sudden death may not be prevented by medical or by surgical therapy in these patients. Surgical therapy consists of surgical excision of the part of the hypertrophic septum (myotomy/myectomy). Concomitant mitral valve replacement may be considered if there is severe mitral regurgitation. The procedure is used primarily in subjects who do not respond to medical therapy and have intractable symptoms. All patients with hypertrophic obstructive cardiomyopathy should receive prophylactic antibiotics before dental or surgical procedures because of the risk of infective endocarditis. Since sudden death occurs most often during or just after strenuous physical exertion, strenuous exercise and sports should be avoided by all patients with hypertrophic cardiomyopathy Anticoagulation may be considered for subjects

who have atrial fibrillation and therefore are at an increased risk of having systemic emboli.

Restrictive Cardiomyopathy

Restrictive cardiomyopathy is characterised by a restriction to ventricular filling during diastole due to excessively rigid ventricular walls with normal or near normal systolic function. According to the World Health Organisation classification of cardiomyopathies, two conditions of unknown cause are included under the category of restrictive cardiomyopathy. These conditions are Loffler's endocarditis and endomyocardial fibrosis (EMF). However, in a more generalised interpretation of the term restrictive cardiomyopathy, myocardial infiltrative disorders of varying etiology can be included under this category. Examples of restrictive cardiomyopathy include amyloidosis, hemochromatosis, glycogen deposition, progressive systemic sclerosis, sarcoidosis and endocardial fibroelastosis.

Pathology and pathophysiology Loffler's endocarditis starts with eosinophilic infiltration of the cardiac muscle and passes through three stages: the necrotic stage, the thrombotic stage, and the fibrotic stage.

The fibrotic stage of Loffler's endocarditis is indistinguishable from endomyocardial fibrosis. In this stage of the disease there is extensive endomyocardial scarring in both disorders. Scarring usually affects either one or both ventricles. The involvement of the atrio-ventricular valves is common, with distortion of the valvular structure, chordae tendineae and papillary muscles, with consequent plastering of portions of the leaflets and improper coaptation. The outflow tracts of the ventricles are usually spared. Cavity obliteration of the ventricles is characteristic of advanced cases. The atria are significantly dilated and may contain thrombi. A pericardial effusion is frequently present and may be large. Apical scarring of both the ventricles may be prominent with retraction of the apices. The pathophysiologic hallmark is impaired diastolic function of one or both ventricles with near normal systolic function and contractility. The ventricular walls are non-compliant and this impedes diastolic filling. Ventricular filling is consequently rapid in the early and middle phase of diastole with little or no further filling in middle and late diastole. This filling pattern represents the cornerstone of the diagnosis and corresponds to the *dip and plateau contour* of early diastolic pressure tracings of the ventricle. This contour of the diastolic portion of the ventricular pressure pulse resembles that in constrictive pericarditis and the two disorders have to be distinguished from each other. Table 12.31 provides a comparison of the features of constrictive pericarditis and restrictive cardio-myopathy represented by endomyocardial fibrosis. The inability of the ventricle to fill during diastole results in elevation of atrial filling pressures which are passively reflected back into the venous circulation. Thus, in dominant left ventricular disease there is elevation of pulmonary venous pressure and in predominant right-sided disease there is elevation of systemic venous pressures. Elevated left-sided filling pressures results in poor exercise tolerance and dyspnea on exertion. Elevated right-sided filling pressures results in peripheral edema, right upper quadrant discomfort due to hepatomegaly and ascites.

Epidemiology Endomyocardial fibrosis occurs most commonly in tropical countries like India and parts of Africa like Uganda and Nigeria. The disorder is also common in Brazil, Columbia and Sri Lanka. In these areas it is a relatively frequent cause of heart failure and a frequent cause of death due to heart failure. The disorder is equally frequent in both sexes and is more common in the younger age group. Loffler's endocarditis probably reflects the variant form of the disease in temperate countries.

Clinical features Combined right and left ventricular endomyocardial fibrosis is a dominant form of the disease followed in frequency by pure right-sided disease; pure left

Table 12.31 Comparison of constrictive pericarditis and restrictive cardiomyopathies

Feature	*Constrictive pericarditis*	*Restrictive cardiomyopathy*
Clinical features		
Orthopnea	unusual	pronounced
Jugular venous pulse	rapid 'x' and 'y' wave descents	normal 'y' descent, large 'v' wave
Apex beat	not prominent	well-defined
Atrioventricular valve regurgitation	unusual	common
Investigations		
Chest X-ray	pericardial calcification	cardiomegaly
ECG	non-specific ST-T changes	LV hypertrophy, bundle branch block
Endomyocardial biopsy	normal	abnormal
Echocardiography	thick pericardium; marked respiratory variation in transmitral Doppler velocities	thickened septum, abnormal echogenicity (in amyloid); atrioventricular valve regurgitation, apical obliteration, dilation of RV outflow tract; absence of respiratory variation in transmitral Doppler velocities
Computerised tomography/MRI	thickened pericardium	normal thickness of pericardium
Catheterisation	• LA pressure = RA pressure = pulmonary wedge pressure; • PA systolic pressure <50 mmHg; • RV end-diastolic pressure > 1/3 RV systolic pressure; • cardiac output mildly decreased	• LA pressure > RA pressure; • PA systolic pressure > 50 mmHg; • RV end-diastolic pressure< 1/3 RV systolic pressure; • cardiac output markedly decreased

LV = left ventricle, RV = right ventricle

ventricular form of EMF is the least common. As mentioned earlier left-sided involvement results in symptoms of pulmonary congestion, while right-sided disease results in symptoms of systemic venous congestion. The arterial pulse is typically narrow in volume. The jugular venous pulse may be elevated with a prominent A wave with rapid x and y descents. The cardiac apex is displaced laterally frequently. Auscultation may commonly reveal third and fourth heart sounds. Murmurs of tricuspid and/or mitral regurgitation are frequently present.

Investigations The electrocardiogram usually shows non-specific abnormalities like diminution of the QRS voltage, non-specific ST-T wave changes, evidence of atrial enlargement and conduction disturbances. On the chest X-ray, the heart size may be increased and a pericardial effusion may be present. There may be evidence of pulmonary venous hypertension. Two-dimensional echocardiography is very helpful in establishing a diagnosis of restrictive cardiomyopathy. The ventricular size is normal and the ventricular systolic function is normal. The ventricular walls are thick and there is often increased reflectivity of the endocardium. The apex of either ventricle is frequently obliterated and both the atria may be significantly dilated as compared to normal or small-size ventricular cavities. A hallmark of the condition is plastering of the atrioventricular valve leaflets along with thickening of the leaflet tissue. Doppler ultrasound reveals evidence of atrioventricular valve regurgitation. A CT scan or MRI may be required to demonstrate the normal thickness of the pericardium to differentiate the disorder from constrictive pericarditis. Endomyocardial biopsy has occasionally been useful in establishing a diagnosis of EMF.

Management The medical treatment of endomyocardial fibrosis is often difficult and is not particularly effective. The use of digitalis glycosides to control the ventricular rate response in patients with atrial fibrillation and the careful use of diuretics in subjects with congestive symptoms have been suggested. In subjects with resistant symptoms, surgery offers the only chance for improvement of symptoms and consists of the operative excision of the fibrotic endocardium with replacement of the atrioventricular valves. Surgery however carries a very high mortality risk in these patients.

KEY CONCEPTS

Dilated cardiomyopathy

- This is a disease of heart muscle characterised by ventricular dilatation and reduced systolic function; by convention, valve disease and coronary artery disease must be absent.
- Dilated cardiomyopathy is most often idiopathic. It may be secondary to alcohol consumption, longstanding hypertension, peripartum state (peripartum cardiomyopathy), drugs (doxorubicin is notorious), viral myocarditis or uremia.
- The symptoms are those of a low cardiac output (fatigue) and left or right-sided venous congestion.
- Cardiac examination reveals cardiomegaly, elevated JVP, loud P_2, left or right ventricular S_3, and murmurs of atrioventricular valve regurgitation.
- The chest X-ray reveals cardiomegaly and varying degrees of pulmonary venous hypertension. The ECG features include low voltage complexes with non-specific ST-T changes, an occasional LBBB pattern and atrial arrhythmias.
- The echocardiogram reveals dilated ventricles with evidence of global hypokinesia. Cardiac catheterisation is usually not required unless coronary disease is to be excluded (patients over the age of 40 years); it reveals elevated LVEDP, reduced EF, diffuse hypokinesia and normal coronaries. An endomyocardial biospy may be contemplated if the history is acute and there is suspicion of myocarditis.
- Management measures include reduction of dietary salt, diuretics, vasodilators (converting enzyme

inhibitors), digitalis (especially if there is atrial fibrillation), and anticoagulants (to reduce risk of embolic episodes). Transplantation is an option for end-stage heart failure.

Hypertrophic cardiomyopathy

- HCM is a cardiac muscle disease characterised by *morphologic* evidence of disproportionate septal *hypertrophy* (septum >1.5 X LVP wall), *histologic* evidence of myofibrillar disarray and *clinical* evidence of diastolic ventricular dysfunction. The disorder may be genetic (autosomal dominant) or sporadic.
- The primary pathophysiologic abnormality in HCM is diastolic dysfunction due to a stiff left ventricle (resulting in elevated LVEDP) with or without evidence of left ventricular outflow tract obstruction. LVOT obstruction is due to the anterior mitral leaflet being drawn towards the LVOT in systole (due to a Bernoulli effect).
- Clinical features include angina-like chest pain, episodic tachyarrhythmias, exertional syncope and breathlessness. HCM may result in sudden cardiac death. HCM is associated with an increased risk of endocarditis. Physical findings include a prominent S_4, an ejection systolic murmur across the LVOT (increasing with Valsalva and decreasing with handgrip), with or without a systolic murmur of mitral regurgitation.
- The ECG findings include evidence of LVH or a pseudoinfarction pattern (deep septal q waves in I, aVL, V_5–V_6); deep T wave inversions in the anterior leads is suggestive of apical variant of HCM (common in Orient). An echocardiogram is the investigation of choice. Echocardiographic features include asymmetrical septal hypertrophy, dynamic LVOT obstruction, systolic anterior motion of the mitral valve (SAM), mid-systolic closure of the aortic valve and mitral regurgitation of a variable degree. A Holter recording may be obtained to screen for (in asymptomatic) or to document in patients with syncope) malignant arrhythmias.
- The medical treatment includes beta-blocking drugs (they slow heart rate and reduce LVOT obstruction), calcium channel blockers (improve diastolic function) and disopyramide (negative inotropic effect). Dual chamber pacing is emerging as an effective alternative. Surgery (myotomy-myomectomy) may be considered in patients with refractory symptoms. Amiodarone is useful for ventricular arrhythmias and reduces the incidence of sudden death. Digitalis should be avoided, and diuretics should be used with caution. Patients are advised to avoid competitive sports.

Restrictive cardiomyopathy

- This is a disease of heart muscles characterised by an increased stiffness of the ventricles and a resultant increased resistance to diastolic filling, systolic function being normal.
- The causes of restrictive cardiomyopathy include infiltrative diseases (sarcoidosis, amyloidosis, glycogen storage diseases, hemochromatosis), radiation and endomyocardial fibrosis (the most important cause in India).
- The clinical features include exertional dyspnea, fatigue and evidence of biventricular failure. Physical findings include lack of cardiomegaly (or enlargement of a mild degree), a prominent S_4, prominent pulsations of the right ventricular outflow tract (in EMF) and murmurs of atrioventricular valve regurgitation.
- The ECG findings include low voltage complexes and ST-T wave changes. Echocardiography reveals dilated atria, thickened ventricles with normal chamber size, and normal systolic pump function. The features of EMF include apical obliteration of the ventricles, tethering of the atrioventricular valve leaflets and dilatation of the RVOT. In amyloidosis, there is a *granular speckled* appearance. An endomyocardial biospy may provide diagnostic information in the case of infiltrative myocardial disease.
- The treatment consists of decongestive measures (diuretics), iron chelation for hemochromatosis, and colchicine for amyloidosis; digitalis should be avoided in cardiac amyloidosis. Endocardial resection with or without tricuspid valve replacement is an adjunctive measure in EMF patients with CHF refractory to medical management.

12.10 Diseases of the pericardium

The pericardium provides a protective sac around the heart and contains a thin layer of fluid (<25 mL) which permits the heart to move with minimal friction during the cardiac cycle. The pericardium restrains the heart when one or more of the cardiac chambers dilate acutely. Pericardial disease results from diverse causes, many of which produce responses to injury which are pathologically and clinically similar. These responses most frequently take the form of acute pericarditis, pericardial effusion or constrictive pericarditis.

Acute Pericarditis

Pericarditis is defined as inflammation of the pericardium. It may be acute, subacute or chronic.

Etiology Acute pericarditis is usually caused by a viral infection. The other causes of pericarditis include bacterial infections (pyogenic pericarditis, tuberculosis), fungal infections, autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis), chronic renal failure, trauma, myocardial infarction, thoracic irradiation, and metastatic neoplasms, especially those of the lung and the breast. In rare cases, drugs may cause pericarditis (procainamide, hydralazine and phenytoin).

Clinical features Inspiratory chest pain is the cardinal symptom of acute pericarditis. Typically the chest pain develops suddenly, is left-sided and may radiate to the neck, shoulders or the trapezius ridge. Chest pain may be mild or severe in intensity. The pleuritic quality, its aggravation by thoracic movement and by coughing, and its partial relief by leaning forward or sitting up are useful clinical features for distinguishing pericardial pain from other causes of chest pain. Occasionally, chest pain may be absent as in uremic, neoplastic or tuberculous pericarditis. Low-grade fever and sinus tachycardia are other usual clinical concomitants. The diagnosis is confirmed by demonstrating the presence of a pericardial friction rub on auscultation. A pericardial friction rub has a scratchy leathery quality and is typically triphasic: systolic and diastolic components are followed by a late-diastolic component which coincides in timing with atrial systole. Often only a diphasic rub can be appreciated. Pericardial rubs are best heard in expiration with the patient leaning forwards.

Investigations Leukocytosis in peripheral blood and elevation of the erythrocyte sedimentation rate are common but relatively non-specific findings. Blood cultures, skin test for tuberculosis and tests for viral antibodies are routinely obtained. The ECG is more often diagnostic and reveals a diffuse ST segment elevation during the first several days of illness; ST segment elevation is present in all leads except those in which the positive electrode faces the ventricular cavity rather than the epicardial surface (such as aVR and sometimes

III or V_1, or both). Depression of the PR segment indicating inflammation of the atrial myocardium, is also seen in acute pericarditis. These changes are related to a diffuse current of injury produced by associated epicardial inflammation. Serial ECGs reveal diffuse T wave inversions (in all leads except aV_R) *after* the ST segment has returned to baseline usually in the second week of disease. The *diffuseness* of the ST segment elevation, the *absence of reciprocal ST segment depression* (in opposite oriented epicardial leads), and the occurrence of T wave changes after the resolution of the ST segment changes distinguish the characteristic pattern of acute pericarditis from the pattern seen in acute myocardial infarction. The pattern of early repolarisation too is associated with ST segment elevation in precordial chest leads and this entity enters into the differential diagnosis. A normal or slow heart rate and tall T waves (relative to the height of the ST segment), and a failure to evolve further in serial ECGs help to distinguish early repolarisation from acute pericarditis.

The chest X-ray reveals enlargement of the cardiac silhouette. An echocardiogram should be obtained routinely in every case of suspected pericarditis; the presence of a pericardial effusion serves as important confirmatory evidence of pericarditis. The presence of fibrinous strands in the effusion may indicate infection by a pyogenic organism *(pyopericardium)*. An important caveat is that the echocardiogram can be normal in pericarditis if there is insufficient effusion. If a significant effusion is present, it may be tapped and sent for microbiologic investigations in an attempt to identify the etiologic agent.

Treatment The treatment is usually directed towards: 1) determining and treating the underlying etiology, 2) observation for the development of pericardial effusion and signs of tamponade, and 3) the relief of chest pain.

Analgesic agents, such as aspirin (650 mg every six to eight hours), codeine (15 to 30 mg orally every four to six hours), indomethacin (25 mg four times daily) often provide adequate relief from pain. Prednisone (20–60 mg/day) will often relieve chest pain and fever which are non-responsive to conventional analgesics. Steroids should be reserved for severe cases and should be used only if a bacterial etiology has been excluded. The pain of acute pericarditis also responds very rapidly to the administration of ketorolac tromethamine, a parenteral non-steroidal antiinflammatory agent. Colchicine (1 mg daily) has been used successfully when acute pericarditis is recurrent.

Pericardial Effusion and Tamponade

Etiology Fluid may accumulate in the pericardial cavity in virtually any form of pericardial disease. The fluid may be a *transudate* as in patients with congestive heart failure, or hypoproteinemia (hepatic cirrhosis or nephrotic syndrome). More often, however, the pericardial effusion is an *exudate* indicating the presence of pericardial injury. Serosanguineous pericardial fluid is pathognomonic of tuberculous and neoplastic disease; this type of effusion also occurs in cases of uremic, radiation-induced and idiopathic pericarditis. Frank blood in the pericardial space (*hemopericardium*) may occur in cases of a ruptured aortic aneurysm or an aortic dissection because of leakage into the pericardial space. Hemopericardium may also be produced by trauma or due to cardiac rupture (in acute myocardial infarction or by the iatrogenic perforation of the cardiac chambers by cardiac catheters). The presence of effused chyle in the pericardial space, or *chylopericardium*, occurs rarely; it is usually a consequence of leakage from the thoracic duct.

Pathophysiology The clinical effects of a pericardial effusion depend on the rapidity of accumulation and the amount of fluid. For example, if the effusion develops gradually, the

pericardium can stretch enough to accommodate a very large effusion with no significant increase in intrapericardial pressure. However, if the effusion develops acutely, even a small volume of pericardial fluid (100 to 200 ml) may cause cardiac tamponade as in the case of hemopericardium caused by trauma. As the pericardial fluid pressure rises from its normal value, which is close to that of atmospheric and intrapleural pressures, the right atrial and central venous pressures rise correspondingly. Thus, the central venous pressure reading is an accurate reflection of the intrapericardial pressure and can be used to determine whether cardiac tamponade is present. Cardiac tamponade should be viewed as a spectrum of hemodynamic abnormalities of varying severity rather than as an all-or-none phenomenon. Depending on the severity of cardiac tamponade, the blood pressure may be reduced or maintained near the normal range. A paradoxic pulse (a greater than normal inspiratory fall in arterial pressure) is the hallmark of cardiac tamponade. It may not be easy to detect on clinical examination. The upper limit of the normal fall in arterial pressure with inspiration is 10 mmHg. Any degree of paradoxic pulse which is perceptible by simple palpation of the radial pulse is abnormal. Pulsus paradoxus is related to augmented inspiratory filling of the right ventricle and the sequestration of blood in the lungs and pulmonary veins as a result of impaired transmission of intrapleural pressure changes to the left atrium and the intrapericardial portions of the pulmonary veins; both these mechanisms limit left ventricular filling. *Kussmaul's sign*[1], or a rise in the level of venous pressure with inspiration, is often mentioned as a sign of cardiac tamponade; however, it occurs only in cases of tamponade associated with constriction and not in uncomplicated tamponade. Loculated pericardial effusions may selectively compress one or more chambers of the heart, producing regional cardiac tamponade; localised cardiac tamponade is usually seen soon after cardiac surgery.

Clinical features The clinical findings of pericardial effusion include chest pain related to associated pericarditis, shortness of breath, tachycardia and a dry cough. The precordial cardiac dullness is increased on percussion and the apical impulse is impalpable. The pericardial friction rub may disappear. The presence of tamponade may be indicated by elevated jugular venous pressure and hepatic enlargement. Large pericardial effusions compress the surrounding lung tissue; an area of dullness to percussion and bronchial breathing at the angle of the left scapula may be present (*Ewart's sign*).

Diagnosis Clinical examination, electrocardiography, chest roentgenography, and fluoroscopy are not very reliable for detecting pericardial effusion. *Electrical alternans* is produced by a beat-to-beat oscillation of the heart from one position to another within the pericardial sac; this is seen only with large effusions. Echocardiography is the most accurate and easily applied method for the clinical detection of pericardial effusions; effusions as small as 20 ml can be detected. Computed tomography is also extremely reliable but should be used only when echocardiography results are inconclusive and clinical suspicion is high. The pericardial fluid must be obtained for diagnostic purposes and analysed for colour, turbidity, cell count, microbial culture and cytology. The technique of pericardiocentesis is discussed in the section on procedures. Serous effusions are common in viral pericarditis, heart failure and hypoalbuminemia. Serosanguineous effusions may be found in tuberculosis and neoplastic infiltration. Chylous effusions may be found after thoracic surgery (if lymph vessels are

[1] While assessing for Kussmaul's sign, the observer must be careful to distinguish a jugular venous pulsation that appears more active with inspiration from a true rise in mean venous pressure.

injured), or in neoplasms infiltrating the lymphatics. The fluid should be characterised as a transudate (protein <3 g/100 ml) or an exudate (>3 g/100 ml). Transudates occur in heart failure, hypoalbuminemia, drug-induced pericarditis, post-pericardiotomy syndrome, and Dressler syndrome.[1] Exudates are more likely in infections, neoplasms, uremia and collagen vascular diseases. The glucose content is low and a polymorphonuclear response is predominant in bacterial pericarditis. The pericardial fluid should be subjected to a Gram stain and Ziehl-Neelsen stain, culture for aerobic, anerobic bacteria and for tuberculosis. Positive cytologic findings can be detected in up to 70 per cent of cases with neoplastic involvement of the pericardium. Tubercular infection is characterised by an exudate with predominant lymphocytes.

Tamponade 'Cardiac tamponade' is a clinical diagnosis based on bedside evaluation. Echocardiographic studies may then be used to support the diagnosis; exaggerated respiratory variation in mitral and tricuspid inflow velocities can be detected by pulsed Doppler ultrasound. An early diastolic inward motion of the wall of the right atrium and right ventricle (inversion) is also a sign of tamponade and can be detected in the echocardiogram.

Treatment of pericardial effusion Treatment of pericardial effusion is dictated by its etiology. Antibiotics are appropriate for pyogenic pericarditis, antitubercular treatment for tubercular effusions, and antiinflammatory agents for viral pericarditis and Dressler syndrome. Steroids have recently been shown to be useful adjuncts in the management of tubercular effusions; they reduce the incidence of constrictive pericarditis.

[1] Pericarditis occurring 3–4 weeks after a myocardial infarction, presumably due to an immunoinflammatory response

Treatment of tamponade Mild cardiac tamponade can be managed conservatively by observation of the patient. When hypotension is present, infusion of fluid or administration of isoproterenol or dobutamine may support the circulation temporarily, but removal of the pericardial fluid is required for definitive treatment. The fluid may be removed by pericardiocentesis, by surgical pericardiostomy with tube drainage, or by limited or extensive pericardiectomy.

Constrictive Pericarditis

Etiology The most important causes of constrictive pericarditis in developing countries are tuberculosis and pyogenic pericarditis. In the developed countries, a majority of cases are idiopathic. Rare causes of constrictive pericarditis include thoracic radiation, rheumatoid arthritis, uremia and prior cardiac surgery.

Pathophysiology In constrictive pericarditis, fibrous scarring and adhesion of both pericardial layers obliterates the pericardial cavity. The pathophysiology of constrictive pericarditis is similar to that of tamponade in that both conditions impede diastolic filling of the heart and lead to increased venous pressure and ultimately to reduced cardiac output. There is one important difference: whereas impairment of cardiac filling is present throughout diastole in tamponade, in constrictive pericarditis early diastolic filling of the ventricle is normal. Hence, an early diastolic dip is prominent in both venous and ventricular pressure tracings in constrictive pericarditis but is not seen in tamponade. Paradoxic pulse is a typical feature of cardiac tamponade but is inconspicuous or absent in constrictive pericarditis. Kussmaul's sign occurs in some patients with constrictive pericarditis but is not seen in patients with pure cardiac tamponade.

Clinical features Clinical manifestations of constrictive pericarditis include shortness of breath and fatiguability due to limitation of cardiac output. Signs of raised right-sided venous pressure include hepatomegaly, ascites and splenomegaly. Dependent edema is less prominent compared to ascites; the typical patient has a distended abdomen but thin extremities (*ascites praecox*). The jugular veins have deep 'x' and 'y' descents. On precordial examination the apical impulse may be impalpable. Heart sounds are typically faint. A diastolic *pericardial knock* may be heard and occurs 0.06 to 0.12 seconds after the onset of aortic closure; it is related to rapid early diastolic ventricular filling.

Diagnosis The clinical diagnosis of constrictive pericarditis depends on the recognition of elevated venous pressure in a patient who does not have other obvious signs or symptoms of heart disease. Constrictive pericarditis presents as an abdominal swelling due to ascites. It is frequently misdiagnosed for prolonged periods as liver disease unless the physician recognises the presence of elevated jugular venous pressure. The ECG usually reveals low voltage QRS complexes with non-specific ST-T wave changes. Atrial fibrillation may be present in upto 25 per cent of cases. The chest X-ray shows a normal or small cardiac silhouette. Cardiac calcification is the diagnostic hallmark on the chest film but is detected in only about 50 per cent of cases; it is more prominent in the lateral chest film and typically occurs in the AV groove and the diaphragmatic surface of the heart. Echocardiography usually shows evidence of pericardial thickening, but this finding is non-specific and does not differentiate constrictive pericarditis from non-constrictive adhesive pericarditis. The CT scan is superior to echocardiography for the demonstration of pericardial thickening; a CT scan that shows a normal pericardial thickness (<7 mm) is usually a reliable indication that constrictive pericarditis is not present. It is occasionally difficult to distinguish constrictive pericarditis from idiopathic restrictive cardiomyopathy; useful pointers in the differentiation are presented in the section on myocardial diseases (Table 12.31).

Treatment Relief of constrictive pericarditis requires surgical stripping and the removal of both layers of the adherent constricting pericardium. Elevated venous pressure should return to normal levels within three months after surgery.

KEY CONCEPTS

Acute pericarditis

- Acute pericarditis is most often infectious in origin; viruses are the predominant agents, although bacterial pericarditis is not uncommon in tropics. The other causes of pericarditis include immunoinflammatory diseases, post-MI (early and late [Dressler syndrome]), uremia, neoplastic infiltration and radiation.
- The most common symptom is acute onset of sharp inspiratory chest pain that decreases on sitting up and with leaning forward. The classical physical sign is a scratchy leathery pericardial friction (which is bi/triphasic).
- The ECG is diagnostic; it reveals diffuse ST segment elevation without concomitant reciprocal ST depression but with concomitant T wave inversions. There may be depression of PR segment. The chest X-ray may reveal a pericardial effusion (water bottle configuration, i.e., cardiomegaly but no pulmonary venous hypertension). An echocardiogram may be diagnostic if it reveals a pericardial effusion. Laboratory investigations include blood cultures (especially if the patient is febrile), ESR and leucocyte count (increased in infections, inflammation), viral serology, serum creatinine, and examination of pericardial fluid (after pericardiocentesis; cytology, biochemistry and microbiology of fluid is vital).
- The treatment is targeted to the cause. NSAIDs are useful for reducing the chest pain generally. Steroids have a role in Dressler syndrome and in

immunoinflammatory disease. Antibiotics and drainage (with a catheter or a surgical window) are indicated in the pyopericardium while antitubercular treatment should be instituted for tubercular pericarditis.

Pericardial effusion with tamponade

- ➢ Tamponade is a condition in which a pericardial effusion compresses the heart and restricts the diastolic ventricular filling with resultant circulatory disturbances. It may arise either when the effusion accumulates rapidly (trauma, aortic dissection, cardiac rupture) or is large (neoplastic, post-surgery).
- ➢ The symptoms of tamponade include dyspnea, fatigue and orthopnea. A pulsus paradoxus (inspiratory fall in systolic blood pressure) of >10 mmHg and narrow pulse pressure suggest significant cardiac compression. The jugular veins may be distended, the pulse rapid and the heart sounds distant.
- ➢ The ECG shows low amplitude complexes with *electrical alternans*. The chest X-ray may reveal a water bottle heart. The echocardiogram provides additional confirmatory evidence of tamponade; the RA and the RV show inversion of the walls/diastolic collapse and the transmitral Doppler reveals excessive respiratory variation.
- ➢ Management consists of immediate pericardiocentesis, administration of i.v. fluids to counter hypovolemia and treatment of the underlying cause.

Constrictive pericarditis

- ➢ Constrictive pericarditis is characterised by the diffuse thickening of the pericardium resulting in the impaired filling of the cardiac chambers. This results in an increase in systemic and pulmonary venous pressure, and a reduction in the cardiac output. Although the condition may be idiopathic, important causes include tuberculosis, pyopericardium, postcardiac surgery, radiation and neoplastic pericardial infiltration.
- ➢ Symptoms include exertional dyspnea, ascites and dependent edema; right-sided symptoms predominate.
- ➢ The findings on physical examination may include inspiratory distension of jugular veins (Kussmaul's sign), tachycardia with a low volume pulse, distant heart sounds and a pericardial knock (early diastolic sound), positive hepatojugular reflux and ascites.
- ➢ The ECG shows low voltage complexes, ST–T wave abnormalities and, occasionally, atrial arrhythmias. The chest X-ray may reveal a normal-sized cardiac silhouette with pericardial calcification; calcification is best seen in the lateral chest film and appears on the diaphragmatic pericardium. The echocardiogram may reveal pericardial thickening (with normal ventricles) but a CT scan or an MRI scan are more reliable for documenting increased pericardial thickness (>7 mm).
- ➢ Cardiac catheterisation shows the typical hemodynamic features: marked x descent, square root sign in the ventricular pressure tracing and equalisation of diastolic atrial and ventricular pressures.
- ➢ Pericardiectomy is the definitive treatment.

12.11 Systemic hypertension

Hypertension or elevation of blood pressure may be defined as any level of increased blood pressure which is associated with cardiovascular morbidity or mortality. Although normal blood pressure has a Gaussian distribution, a level of systolic blood pressure greater than or equal to 140 mmHg or a diastolic blood pressure greater than or equal to 90 mmHg have been arbitrarily defined as indicative of hypertension in adults. Criteria for hypertension in children and adolescents have also been formulated. The following levels are associated with significant risk in children: 116/76 mmHg (three to five years of age); 122/78 mmHg (six to nine years of age); 126/82 mmHg (10 to 12 years of age); 136/86 mmHg (13 to 15 years of age); and 142/92 mmHg (16 to 18 years of age).

Classification Table 12.32 summarises a classification of hypertension in adults suggested by the World Health Organisation in 1993. The fifth Joint National Committee on Detection, Education and Treatment of high blood pressure of the USA (JNC V) has suggested an alternative classification which is slightly different from this but this second classification is not presented here for the sake of simplicity.

Pathogenesis The pathogenesis of hypertension is mutifactorial. Genetic factors, shared familial factors and environmental influences all determine the blood pressure of an individual. Recently a blood pressure regulatory locus has been identified in chromosome 1q4 in humans. Additionally, increased salt intake, defects in

Table 12.32 WHO classification of hypertension

Category	*Systolic blood pressure (mmHg)*		*Diastolic blood pressure (mmHg)*
Normotension	<140	and	<90
Mild hypertension	140–180	and/or	90–105
Borderline hypertension	140–160	and/or	90–95
Moderate and severe hypertension	>180	and/or	>105
Isolated systolic hypertension (ISH)	>140	and	<90
Borderline ISH	140–160	and	<90

renal excretion of sodium, abnormalities of transcellular ion transport resulting in elevation of intracellular sodium and calcium levels in vascular smooth muscle cells have all been implicated. Whatever the pathogenic mechanisms, there is an elevation of peripheral vascular resistance, with or without an associated increase in cardiac output. The sympathetic nervous system and the renin-angiotensinogen system have received the most attention as both can increase cardiac output and peripheral resistance. Obesity and alcohol intake are two additional influences that contribute to elevation of blood pressure. The relation of increased stress to high blood pressure, although likely, has been less well substantiated. The secondary causes of hypertension include renal disease (arterial or parenchymal), endocrine disturbances (Cushing's disease, phaeochromocytoma, thyrotoxicosis, primary aldosteronism) and coarctation of the aorta. Systolic hypertension in the elderly has a different pathogenesis as compared to that described previously; increased compliance of large arteries plays a central role.

Sequelae The World Health Organisation has classified hypertension-related end-organ damage into three stages (Table 12.33); this staging does not refer to the severity of blood pressure elevation but to the presence or absence of hypertensive target organ damage. Chronic hypertension leads to left ventricular hypertrophy, which is associated with diastolic ventricular dysfunction, and in late stages, with systolic ventricular dysfunction. Severe hypertrophy predisposes to coronary atherosclerosis and myocardial ischemia. Congestive heart failure, ventricular arrhythmias and sudden death have been associated with left ventricular hypertrophy. Renal impairment known as *hypertensive nephrosclerosis* may ensue if blood pressure is elevated for prolonged durations. The cerebral vasculature is affected by hypertension and there is an increased propensity for stroke from vascular thrombosis, or from hemorrhages from small microaneurysms of penetrating intracerebral arteries. Hypertensive encephalopathy is probably related to acute capillary congestion and exudation with cerebral edema.

Prevalence In Europe and USA it is estimated that upto 25 per cent of the general population is hypertensive. Estimates from the Indian subcontinent are similar. The prevalence of diastolic hypertension increases with age before levelling off at 55 to 60 years. Systolic hypertension increases from the age of 55 years onwards and is the most common type of hypertension in the elderly. Almost 85 to 90 per cent of hypertension is 'essential' (meaning with no identifiable secondary cause). About 5 to 10 per cent of cases are secondary to renal parenchymal disease; only 1 to 2 per cent of patients have a potentially curable cause of hypertension.

Clinical features Mild to moderate hypertension is not associated with any symptoms.[1] Suboccipital pulsating early morning headaches are typical but uncommon, although any type of headache may occur. Accelerated hypertension is associated with confusion, visual disturbances, nausea and vomiting. Paroxysmal hypertension suggests an adrenal cause of hypertension. Recurrent episodes of generalised muscular weakness may suggest mineralocorticoid excess.

Evaluation The initial evaluation of the hypertensive patient has three objectives: 1) to define the severity of hypertension; 2) to search for clues of secondary causes of hypertension; and 3) to determine the presence or absence of end-organ damage and other risk factors for cardiovascular disease. Before a diagnosis of hypertension is established, blood pressure should be measured on at least two occasions unless the initial values are higher than

[1] Hence the term 'silent killer'

Table 12.33 WHO classification of stages of hypertension

Stage I:	No objective signs of organic changes
Stage II:	At least one of the following signs of organ involvement :
	• left ventricular hypertrophy (X-ray, electrocardiography, echocardiography)
	• generalised and focal narrowing of the retinal arteries
	• proteinuria and/or slight elevation of plasma creatinine (1.2-2.0 mg/dl)
	• ultrasound or radiological evidence of atherosclerotic plaque (carotid arteries, aorta, iliac and femoral arteries)
Stage III:	Both symptoms and signs of organ damage:
	• heart: angina pectoris, myocardial infarction, heart failure
	• brain: transient ischemic attack, stroke, hypertensive encephalopathy
	• optic fundi: retinal hemorrhage, exudates with or without papilledema
	• kidney: plasma creatinine above 2 mg/dl, renal failure
	• vessels: dissecting aneurysm, symptomatic arterial occlusive disease

150–160/105–110 mmHg, in which case treatment is justified without additional recordings. Individuals who are initially hypertensive but become normotensive on follow-up should be carefully reassessed at intervals of six months.

Every hypertensive patient should be evaluated for the presence of secondary hypertension. Renovascular hypertension should be suspected in : 1) new-onset hypertension in a person over the age of 50–60 years or in a preadolescent subject; 2) patients with severe hypertension refractory to treatment; 3) patients with diastolic blood pressure more than 110 mmHg and a negative family history of hypertension; and 4) patients, especially younger women, who have a periumbilical renal artery bruit (characteristically holosystolic with a short diastolic component).

A history of muscle weakness or cramps should lead to suspicion of primary hyperaldosteronism; a serum potassium level below 3.5 mEq/L in the absence of diuretic treatment should strengthen this suspicion. The presence of truncal obesity, excess body hair and abdominal striae should suggest a diagnosis of hyperadrenocorticism (Cushing's disease). A phaeochromocytoma or a hyperthyroid state should be suspected from a history of palpitations, headaches, weight loss, tremors and orthostatic hypotension. The absence or decrease of femoral arterial pulses, the presence of a short systolic precordial murmur, the presence of systolic bruits over the spine and interscapular region, and the palpation of arterial collaterals should suggest coarctation of the aorta. It is also important to obtain a drug history. Several drugs can elevate blood pressure, although the degree of elevation is usually mild and the overall contribution to hypertension by drugs is quite small. Drugs that elevate blood pressure include high dose estrogens, adrenal steroids, non steroidal antiinflammatory agents, several cold remedies, cyclosporin and tricyclic antidepressants.

Physical examination should include measurement of blood pressure in both arms and the legs. Fundoscopic examination is also important although it may not be helpful in the majority of subjects with Stage I–II

hypertension. The presence of arteriovenous nicking suggests that the blood pressure has been elevated for a considerable length of time. The presence of flame-shaped hemorrhages, exudates or papilledema suggest end-organ damage and indicate a poor prognosis if untreated.[1] Precordial examination should include palpation for a forceful apex beat that may indicate left ventricular hypertrophy. An accentuated aortic component of second heart sound is frequently present when the diastolic blood pressure is above 100 mmHg. A third or fourth heart sound suggests poor cardiac function or atrial enlargement, respectively. Specific cardiac murmurs are not present; a diastolic murmur of aortic regurgitation may occasionally be heard with marked elevation of blood pressure and aortic ring dilatation. Examination of the peripheral pulses and auscultation for abdominal bruits should be part of the routine evaluation of any hypertensive subject due to the reasons mentioned earlier.

The initial laboratory evaluation of the hypertensive subject need not be extensive. A routine urinalysis, blood electrolytes, blood urea (or serum creatinine) and an ECG should be obtained. If proteinuria is absent, a renal cause of hypertension is unlikely. White or red cell casts suggest the presence of accelerated hypertension, malignant hypertension, chronic glomerulonephritis, or pyelonephritis.

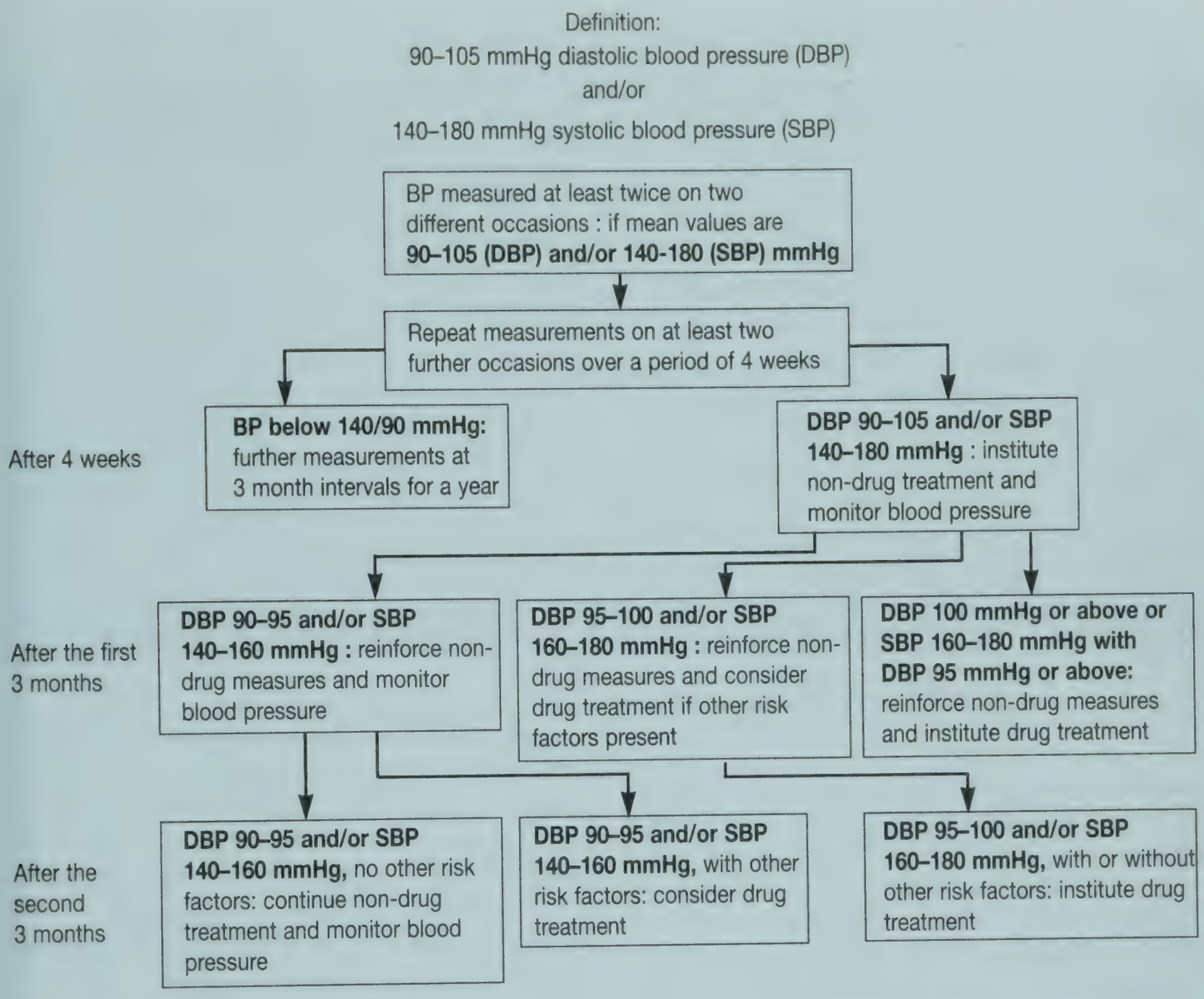
The chest X-ray, IVP, and plasma renin are not currently recommended as routine investigative procedures in hypertensive subjects unless a high suspicion of secondary hypertension is present.

Treatment The initial approach to a subject with mildly elevated blood pressure is depicted in Fig 12.35. The decision to treat depends on the level of blood pressure elevation and the presence or absence of other concomitant risk factors. The goals of treatment of hypertension are to reduce blood pressure to a level below 140 mmHg systolic, and below 90 mmHg diastolic. Randomised clinical trials have shown that a 5 mmHg reduction in diastolic blood pressure (and a 10 mmHg reduction in systolic pressure) reduces the risk of stroke by about a third and the risk of coronary events by a sixth. Blood pressure treatment is more imperative in men, in subjects with a family history of cardiac disease, in those with previous cardiac disease or with the concomitant presence of risk factors such as hypercholesterolemia, diabetes or smoking. In developing countries, population-based initiatives to reduce average blood pressure of the population would be worthwhile. The choice of drugs should be made carefully with emphasis on cost-effectiveness. Trial of several non-pharmacologic interventions is recommended as an initial measure in patients with mild hypertension. Weight reduction in overweight subjects, reduction in alcohol consumption to no more than 20–30 g of ethanol per day, regular mild exercise in sedentary subjects, and sodium chloride restriction to no more than 5 g/day are all effective measures for lowering mildly elevated levels of blood pressure.

Several classes of drugs can be recommended as first-line treatment of mild sustained hypertension. They may be listed in order of proven benefit (based on clinical trial data on morbidity-mortality reduction): 1) diuretics, 2) beta-blocking drugs, 3) angiotensin-converting enzyme inhibitors, 4) calcium channel antagonists, 5) alpha adrenoceptor blocking drugs. Certain classes of drugs may be preferred under certain conditions (Table 12.34). The use of relatively inexpensive agents and those that need be taken only once daily are preferred as they augment patient compliance.

Severe hypertension is usually divided into two categories based on the promptness with which lowering of blood pressure is necessary.

[1] Keith, Wagener, and Barker classified retinal arteriolar changes in hypertension into 4 grades: Grade 1: arteriolar constriction, Grade 2: constriction and sclerosis of arterioles, Grade 3: hemorrhages and exudates, and Grade 4: papilledema.



N.B. Institute drug treatment more promptly in patients with evidence of substantial risk of cardiovascular disease or in patients with blood pressure above the mild hypertension range.

Fig 12.68 Definition and management of mild hypertension

Hypertensive urgencies are situations where the blood pressure is considerably elevated but symptoms and signs of end-organ damage are absent; immediate initiation of rapidly acting oral agents is usually sufficient. *Hypertensive emergencies* refer to situations where there is imminent danger of death or serious morbidity; parenteral treatment must be initiated immediately. Emergencies include hypertensive encephalopathy (headache, altered sensorium and severe hypertension), aortic dissection, preeclampsia-eclampsia, and malignant hypertension (severe hypertension plus encephalopathy or nephropathy and papilledema). The treatment of hypertensive urgencies and emergencies is listed in Table 12.35.

Drug treatment Drugs used to treat hypertension include diuretics, sympatholytics, vasodilators, angiotensin-converting enzyme

Table 12.34 Antihypertensive drug therapy, individualisation based on special considerations

Clinical situation	*Preferred*	*Relatively or absolutely contraindicated*
Angina pectoris	Beta-blockers: Calcium antagonists	Direct vasodilators
Cardiac failure	ACE inhibitors Diuretics	Beta blockers; Calcium antagonists
Hypertrophic cardio-myopathy with severe diastolic dysfunction	Beta-blockers, Diltiazem; Verapamil	Diuretics, Alpha1 blockers; ACE inhibitors, Hydralazine; Minoxidil
Post-MI	Non-ISA beta-blockers, ACE inhibitors	Direct vasodilators
Peripheral vascular occlusive disease	None	Beta-blockers

MI = myocardial infarction, ISA = intrinsic sympathomimetic activity, ACE = angiotensin converting enzyme

inhibitors, and calcium channel blockers (Table 12.36).

Diuretics: There are three classes of diuretics that have been used as antihypertensive agents: thiazides, loop diuretics and potassium-sparing diuretics. Of these, thiazides have been the most popular agents. They have the following significant metabolic side effects: hypokalemia, hyperlipidemia, hyperglycemia, hyperuricemia and hypercalcemia. Diuretic hypokalemia is related to the duration of action of the agent; longer acting agents induce more profound kaliuresis. Serum potassium must, therefore, be measured after initiating diuretic therapy. If hypokalemia develops, supplementary potassium or a potassium-sparing diuretic should be administered. Thiazides can also alter the lipid profile unfavourably by increasing LDL cholesterol and triglyceride levels. Diabetic patients must be monitored for a worsening of glycemic control. Hypercalcemia of greater than a mild degree is rarely caused by thiazides and should prompt a search for hyperparathyroidism. Indapamide is a newer thiazide-like diuretic with a safer metabolic profile.

Loop diuretics are less effective as antihypertensive agents because of their shorter duration of action. These agents (furosemide, ethacrynic acid and bumetanide) should be reserved for patients with evidence of moderate to severe renal insufficiency (in whom thiazides are ineffective), and for patients with documented allergy to thiazides. Metolazone may also be effective in those patients who have reduced creatinine clearance.

Potassium-sparing diuretics are less potent than other diuretics and are reserved for patients with mineralocorticoid-induced hypertension, or those with significant diuretic-induced hypokalemia. Extreme caution should be exercised in diabetic patients, in patients with impaired renal function, and in patients receiving an ACE inhibitor. Triamterene should be avoided in patients with a history of renal calculus disease.

Sympatholytic agents :

Beta-blockers: Beta-blockers are also recommended for use as initial therapeutic agents for the treatment of hypertension. Single-drug therapy with a beta-blocker appears to be

Table 12.35 Management of hypertensive urgencies and emergencies

Drug	*Dosage*	*Onset*	*Duration*	*Adverse effects*	*Comments*
Hypertensive emergencies (parenteral agents)					
Sodium nitroprusside	0.25–10 μg/kg/min as i.v. infusion	seconds	3–5 minutes	nausea. vomiting, muscle twitching; thiocyanate and cyanide toxicity on prolonged use; methemoglobinemia acidosis	most effective; infusion set must be light-resistant
Nitroglycerin	0.25–5 μg/kg/min as i.v. infusion	2–5 minutes	3–5 minutes	headache, flushing, tachycardia, methemoglobinemia	tolerance may develop
Diazoxide	50–150 mg i.v. bolus repeated at 5–15 min intervals, 15–30 mg/min infusion	1–2 minutes	4–24 hours	hypotension, hyperglycemia, aggravation of angina	avoid extravasation
Labetalol	20–40 mg every 10 mins, maximum of 300 mg; infusion 0.5–2 mg/kg/min	5–10 minutes	3–6 hours	bronchoconstriction, heart block, postural hypotension	avoid in CHF, asthma
Hydralazine	5–20 mg i.v. or i.m., can repeat after 20 minutes	10–30 minutes	2–6 hours	tachycardia, headache	avoid in aortic dissection, severe angina
Hypertensive urgencies (oral agents)					
Nifedipine (not extended release)	10–20 mg oral, repeat after 30 minutes	15 minutes	2–6 hours	hypotension, tachycardia, headache	can be given sublingual but with careful watch for precipitous fall in blood pressure
Captopril	25 mg oral	15–30 minutes	4–6 hours	excess hypotension	contraindicated in bilateral renal artery stenosis
Clonidine	0.1–0.2 mg oral, repeated every hour (maximum dose of 0.6 mg)	30–60 minutes	6–8 hours	sedation	rebound hypertension may occur
Labetalol	200–400 mg oral, repeat every 2–3 hours	30 minutes–2 hours	6 hours	bronchoconstriction, heart block, postural hypotension	avoid in CHF, asthma

Table 12.36 Drugs for the treatment of hypertension

Drug	*Daily dose (mg)*	*Duration of action (hours)*	*Side effects*	*Comments*
I. Thiazide diuretics				
Bendroflumethiazide	5–20	6–12		
Hydrochlorthiazide	12.5–50	12–18	hypokalemia, hyperuricemia, glucose intolerance, hyperlipidemia, weakness, rash	may be ineffective in renal impairment (metolazone is effective); consider potassium replacement
Chlorothiazide	250–500	6–12		
Benzthiazide	25–50	12–18		
Chlorthalidone	12.5–50	24–72		
Metolazone	2.5–5	12–24		
II. Loop Diuretics				
Furosemide	20–500	3–6	same as for thiazides	are shorter acting (not ideal antihypertensive agents); effective in renal failure
Ethacrynic acid	25–300	3–6		
Bumetanide	0.5–2	4–6		
III. Potassium-sparing diuretics				
Spironolactone	25–100	6–12		danger in renal failure, and combination with ACE-inhibitor, NSAID;
Triamterene	50–150	6–12	hyperkalemia	increases lithium levels
Amiloride	5–10	24		
IV. Centrally-acting α_2 agonists				
Methyldopa	250–2000	6–12	drowsiness, dry mouth, sedation, fatigue, sexual dysfunction	rebound hypertension with abrupt discontinuation, care in combination with beta-blockers
Clonidine	0.2–0.8	6–12		
Clonidine patch	1 patch (0.1, 0.2. 0.3)	weekly		
Guanabenz	4–64	8–12		

Table 12.36 Drugs for the treatment of hypertension (contd.)

Drug	*Daily dose (mg)*	*Duration of action (hours)*	*Side effects*	*Comments*
V. α_1-adrenergic blockers				
Prazosin	2–20	3–6		
Doxazosin	2–16	24	'first-dose' syncope, orthostatic hypotension,	caution in elderly
Terazosin	1–20	24	weakness, headache	
VI. Peripherally-acting adrenergic antagonist				
Guanethidine	10–200	24	diarrhea, sexual dysfunction, orthostatic	
Guanadrel	10–100	8	hypotension,	
Rauwolfia alkaloids	0.1–0.25	24	lethargy, nasal congestion, depression	caution in patients with depression, peptic ulcer
VII. Beta-adrenergic blockers				
Propranolol	40–640	6–12		
Metoprolol	100–400	12	bronchospasm, fatigue, sexual dysfunction,	care in COPD, CHF, AV-block, diabetics,
Atenolol	50–100	24	worsening of CHF, mask symptoms of hypoglycemia	peripheral vascular disease
Acebutalol	400–1200	12–24		
Pindolol	10–60	6–12		
Labetalol	200–800	3–6		combined α+ß blockade
VIII. Angiotensin-converting enzyme inhibitors				
Captopril	25–300	4–8	cough, rash, angioneurotic edema,	'first-dose' hypotension, care in
Enalapril	5–40	12–24	dysgeusia, hyperkalemia	renal failure (monitor serum K^+), contraindicated in bilateral renal
Lisinopril	5–40	24		artery stenosis

Table 12.36 Drugs for the treatment of hypertension (contd.)

Drug	*Daily dose (mg)*	*Duration of action (hours)*	*Side effects*	*Comments*
IX. Vasodilators				
Hydralazine	20–300	6	positive ANA	
Minoxidil	5–10	24–72	hypertrichosis	can aggravate pleural effusions
X. Calcium channel blocking agents				
Diltiazem	120–360	6–8	asthenia, pedal edema, bradycardia, worsening of CHF	Avoid in CHF, AV-blocks bradyarrhythmias
Diltiazem sustained release	120–360	12		
Verapamil	120–480	6–8	above + constipation	
Verapamil sustained release	120–480	12–24		
Nifedipine	30–180	6–8	pedal edema, headache, dizziness, flushing, tachycardia	
Nifedipine sustained release	30–90	24		

most effective in young and middle-aged patients, and in those with concomitant angina pectoris. Beta-blockers can be non-selective (propranolol), cardioselective (atenolol, metoprolol, acebutalol), with intrinsic sympathomimetic activity (pindolol, oxprenolol, acebutalol), vasodilatory (celiprolol) and with longer duration of action (sotalol, nadolol).

Treatment with beta-blockers involves certain risks. Patients with heart failure, bradycardia, second or third degree heart block, or asthma can usually tolerate only modest doses of beta-blockers. Some of these side effects are avoided by using certain agents with cardioselective action or with intrinsic sympathomimetc activity (ISA).

Propranolol has been used for the longest duration of time and has proven to be safe over the years. The initial dose is 20 to 40 mg twice a day followed by a gradual increase until the desired level of blood pressure is achieved. The side effects of propranolol increase in a dose-related manner and become significant at doses exceeding 240–360 mg/day. Metoprolol and atenolol are selective beta-1 antagonists with efficacies comparable to that of propranolol; they have less risk of exacerbating bronchospasm since they are better tolerated by patients with asthma or obstructive pulmonary disease. Cardioselective agents may also be preferred in patients with insulin-dependent diabetes mellitus since they intefere less with the beta receptor-mediated response to hypoglycemia, and may also be advantageous in patients with peripheral vascular disease since they do not raise systemic vascular resistance. A 50 mg dose of metoprolol is equivalent to a 40 mg dose of propranolol. Agents with intrinsic sympatho-mimetic activity produce less bradycardia (safe in those with brady-arrhythmias), and may be used in patients with a history of congestive heart failure, peripheral vascular insufficiency or asthma.

Alpha-blockers: *Methyldopa* — Although methyldopa has been used for a long time, significant side effects including orthostatic hypotension, decreased alertness and depression have limited its popularity as an antihypertensive agent. Methyldopa acts by producing a false neurotransmitter.

Clonidine — Clonidine, a central $alpha_2$-adrenergic agonist, is an extremely effective antihypertensive agent with a side effect profile similar to methyldopa (although orthostatic hypotension is uncommon). The risk of rebound hypertension if the drug is discontinued suddenly is of specific concern. It is an excellent choice for the hypertensive smoker because of its use for smoking cessation, an action related to its inhibition of CNS sympathetic output.

Combined alpha-and beta-blocking drugs: *Labetalol* — Labetalol combines both alpha-and beta-blocking properties. Its alpha-blocking effects result in less bradycardia and a lesser degree of negative inotropy than that caused by other beta blockers. However, the same alpha-blocking properties lead to postural hypotension and retrograde ejaculation. An intravenous form of labetalol is used for treating hypertensive emergencies.

$Alpha_1$ adrenergic blockers: *Prazosin* —Prazosin blocks postsynaptic $alpha_1$ receptors. Prazosin has a high patient acceptance and has been successfully used as a secondary agent in combination with a diuretic for the treatment of young patients with moderately severe hypertension. Terazosin and doxazosin are newer $alpha_1$ receptor inhibitors with comparable effects.

Vasodilating agents: *Hydralazine* —Hydralazine is commonly used in combination with a beta-blocker and a diuretic; in combination, it is highly effective and its side effects are minimal. *Minoxidil* — Minoxidil is more potent than hydralazine. The most limiting side effect has been hypertrichosis.

Angiotensin-converting enzyme (ACE) inhibitors: Agents of this group inhibit the enzyme that converts angiotensin I to

angiotensin II. They reduce peripheral resistance and, therefore, reduce left ventricular afterload. There is some evidence to suggest that drugs in this class are more effective and possibly safer than other antihypertensive drugs for the treatment of hypertension in diabetics. Because ACE inhibitors interfere with the production of aldosterone (by inhibiting formation of angiotensin II), they may produce hyperkalemia, especially in patients with renal insufficiency. They are contraindicated in patients with suspected bilateral renal artery stenosis.

Captopril — Captopril was the first approved member of this class. Captopril is effective as monotherapy in patients with hypertension. The initial dose should be 6.25–12.5 mg to assess patient tolerance and to minimise 'first-dose' hypotension. Cough is the most common side effect of captopril and other ACE inhibitors. Less common side effects include a rash (in 10 per cent), alteration or loss of taste (dysgeusia) in 2–4 per cent, proteinuria (in one per cent), and granulocytopenia (0.01 per cent).

Enalapril — Enalapril is an effective antihypertensive agent which is extremely well tolerated; renal insufficiency and severe granulocytopenia have been noted less often than with captopril and the drug is effective when taken once a day.

Calcium channel blockers: Calcium channel blockers act as arteriolar vasodilators by lowering the increased levels of calcium in the vascular smooth muscle of hypertensives. These drugs have been particularly successful in treating hypertension in the elderly, African-American patients. Nifedipine has proven useful for treating hypertensive emergencies.

Dihydropyridines — Nifedipine is the prototype dihydropyridine. Initial use of short acting preparations was associated with frequent side effects such as flushing, headaches, and postural hypotension; longer-acting forms virtually lack most of these side effects. Other calcium channel blockers of the dihydropyridine class include amlodipine, felodipine, isradipine, and nicardipine; their efficacy and side effects are similar to those of nifedipine.

Non-dihydropyridine calcium blockers Diltiazem and verapamil are non-dihydropyridine calcium antagonists that are available in standard and long-acting formulations. These agents differ from the dihydropyridines primarily in their negative chronotropic effect; they should be avoided or used only with great caution in patients who have conduction abnormalities and in patients using beta-blockers.

Secondary hypertension

About 10 per cent of hypertension is related to a secondary cause. Renal parenchymal, renovascular and endocrine causes account for most secondary hypertension. Chronic parenchymal renal disease and endocrine causes of hypertension (mineralocorticoid or catecholamine excess states) are discussed in the corresponding sections. A brief description of renovascular hypertension is provided below.

In renovascular hypertension one or both of the renal arteries are narrowed. The resultant renal ischemia leads to stimulation of the renin-angiotensin system with consequent elevation of blood pressure. The renal arterial stenotic lesions may occur due to one of three causes: 1) *fibromuscular dysplasia* is characterised by proliferation of vascular media and is seen in young women; 2) atherosclerotic narrowing of the proximal renal arteries is encountered in older men; and 3) Takayasu's arteritis (non-specific aortoarteritis), which is especially important in the Indian subcontinent.

The screening tests for renovascular hypertension include abdominal ultrasound and captopril renogram. The captopril renogram measures the renal uptake of a radiolabelled compound before and after captopril administration. A positive test suggests the need for performing more definitive tests. A definitive diagnosis requires a renal arteriogram to assess vascular anatomy and selective renal vein renin level estimation (to confirm the activation of the

renin-angiotensinogen system on the side of the stenosed vessel, with contralateral suppression). The treatment options include angioplasty for discrete lesions and medical treatment or surgical revascularisation for diffuse lesions. Converting enzyme inhibitors are contraindicated in patients with bilateral renal artery stenosis.

KEY CONCEPTS

- Hypertension is defined as a systolic blood pressure ≥140 mmHg, or a diastolic blood pressure ≥90 mmHg.
- The hemodynamic basis of hypertension is an elevation of peripheral vascular resistance or cardiac output (or both). It reflects the complex interaction of the sympathetic nervous system and the renin-angiotensin system.
- A majority (90%) of cases are essential (without an underlying causal disease). The combined influences of genetic, familial and environmental factors contribute to the pathogenesis.
- Important secondary causes of hypertension include renal disease (renovascular or renal parenchymal), endocrine conditions (Conn syndrome, Cushing syndrome, pheochromocytoma, acromegaly), drugs (oral contraceptives, steroids) and miscellaneous conditions (polycythemia, aortic coarctation).
- The complications of systemic hypertension include LVH, retinopathy, cerebrovascular disease, CHF, atherosclerosis and nephrosclerosis.
- Hypertension is usually asymptomatic; diagnosis depends on detection by screening. The initial physical examination should include measurement of blood pressure in both the upper and one of the lower extremities. Additional findings may include an LV apical impulse, a loud A_2 and an S_4.
- The routine investigations include renal biochemical parameters, urinalysis, serum potassium and ECG. If secondary hypertension is likely, the following tests may be considered: captopril renogram (suspected renovascular hypertension; HTN at extremes of age, refractory hypertension, the presence of abdominal bruit), urinary catecholamines (pheochromocytoma), plasma renin and aldosterone (Conn syndrome), and urinary free cortisol (Cushing syndrome).
- Clinical trials of hypertensive patients have clearly shown a reduction in mortality and morbidity associated with coronary artery disease, strokes and CHF.
- The treatment is often initiated with non-pharmacologic means: weight reduction, reduced dietary sodium (<2 g/d), reduced alcohol intake (<1 oz/d), smoking cessation, regular exercise, and dietary potassium and calcium supplementation. Pharmacologic measures include choosing from a variety of drugs of comparable efficacy: diuretics, beta-blockers, alpha-blockers, converting enzyme inhibitors, and calcium channel antagonists; the choice is individualised based on patient factors (age, race, associated disease) and preferences.
- Hypertensive *emergencies* include conditions with markedly elevated blood pressure where there is an imminent danger to life (hypertensive encephalopathy, LVF). Treatment with intravenous agents (diazoxide, labetalol, nitroprusside, nitroglycerin) is recommended. Hypertensive *urgencies* (blood pressure considerably elevated but no end organ damage) can be managed with oral antihypertensive agents (nifedipine, captopril, labetalol, clonidine).

12.12 Diseases of the aorta and peripheral vessels

ANEURYSMS OF THE AORTA

Aneurysm of the Thoracic Aorta

An aneurysm is defined as an abnormal dilatation of a vessel that includes the endothelial layer of the vessel. This definition identifies a true aneurysm as opposed to a false aneurysm, wherein the wall includes the media and the adventitia but not the intima.

Pathogenesis Aneurysms may occur in any segment of the thoracic aorta. Atherosclerosis and medial degeneration are the two most frequent causes. Other rarer causes include the Marfan syndrome, non-specific aortitis and tertiary syphilis. Atherosclerosis is associated more often with aneurysms of the descending thoracic aorta, whereas medial degeneration is associated more often with aneurysms of the ascending aorta. Systemic hypertension is a prominent predisposing factor for aortic aneurysms irrespective of their location. Thoracic trauma can also lead to a descending thoracic aortic aneurysm; most posttraumatic aneurysms arise at a point just distal to the origin of the left subclavian artery because the aorta is fixed at this site.

Aortic aneurysms can be fusiform or saccular (Fig 12.36). A diffuse fusiform dilatation is one kind of aneurysmal enlargement of the ascending aorta. Fusiform dilatation of the ascending thoracic aorta associated with aortic valvular regurgitation is known as *annuloaortic*

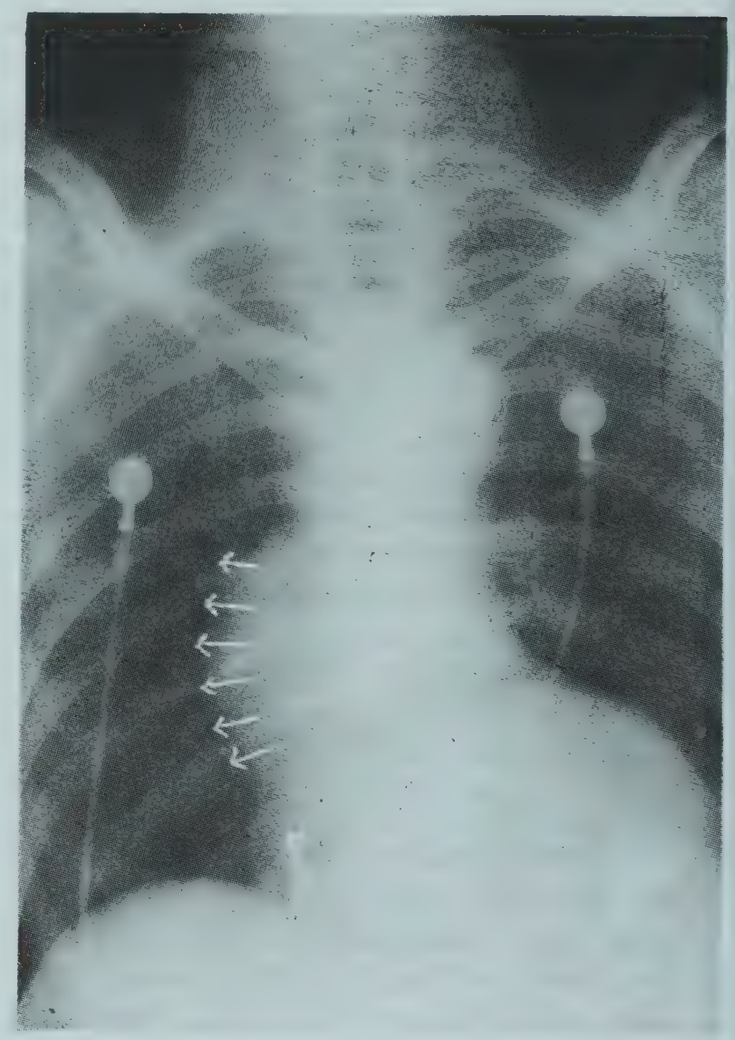


Fig 12.69 Plain X-ray chest (PA view) of a 75-year old man with long standing systemic hypertension. The arrows indicate an aneurysm of the ascending aorta, the curved single arrow indicates the calcific aortic knuckle. There is enlargement of the heart (LV contour). The patient had hypertensive heart disease. The single straight arrow at the bottom of the skiagram shows part of a temporary pacemaker lead. This patient also had complete heart block that required pacing. The heart block was presumably due to sclerodegenerative changes in the conduction system (not attributable to hypertension)

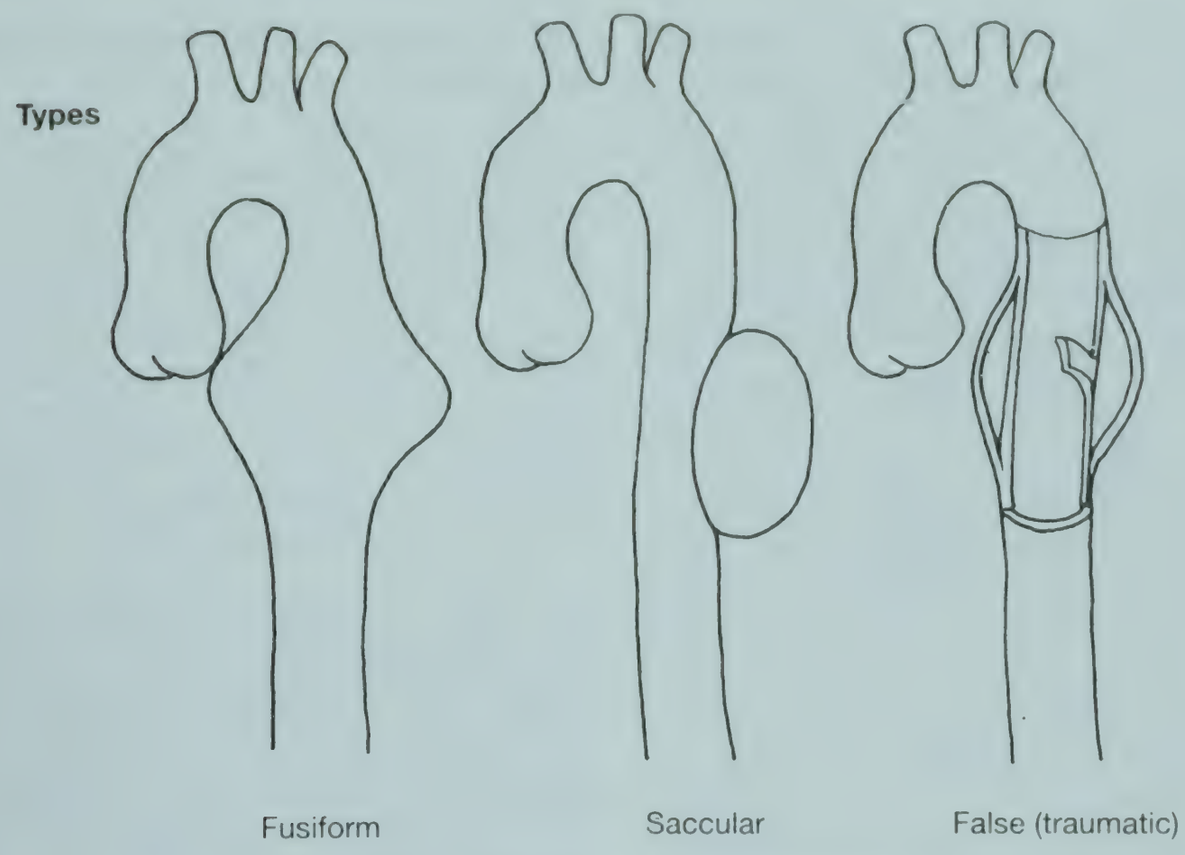


Fig 12.70 Types of thoracic aortic aneurysms
Fusiform and saccular aneurysms constitute the most frequent morphologic types.

ectasia. A saccular aneurysm arises as an eccentric bulge from one side of the aortic wall. Irrespective of their location or their morphology, aortic aneurysms tend to expand progressively and eventually rupture. The probability of rupture increases greatly when the diameter of the aneurysm exceeds 8 cm, although smaller aortic aneurysms can and do rupture.

Clinical features Aneurysms of the ascending aorta are usually discovered on routine chest X-ray (Fig 12.69) or are recognised due to associated aortic regurgitation arising from annular dilatation. Arch aneurysms are the most symptomatic of thoracic aortic aneurysms due to their proximity to several intrathoracic structures. Compression of the recurrent laryngeal nerve can cause hoarseness of voice, pressure on the superior vena cava can result in facial edema and venous distension, whereas tracheobronchial compression may manifest as wheezing or dyspnea. Atherosclerotic aneurysms involving the descending thoracic aorta are often asymptomatic. Rupture of a thoracic aortic aneurysm presents with catastrophic onset of chest pain and circulatory collapse.

Investigations Cardiac computerised tomography (CT), magnetic resonance imaging (MRI) and aortography are all reasonable approaches to investigating a patient with a suspected aortic aneurysm. Cardiac catheterisation may also be required to exclude associated coronary artery disease if surgery is contemplated. Echocardiography is useful for evaluating aneurysms of the proximal ascending thoracic aorta.

Treatment Small thoracic aneurysms can be followed up medically with serial CT or MRI studies every 6 to 12 months. Patients with Marfan syndrome should be started on lifelong beta-blocker therapy as soon as they develop dilatation of the aortic root. Surgical resection of

thoracic aortic aneurysms must be considered whenever local pressure symptoms, such as chest pain or back pain are prominent, when progressive enlargement of the aneurysm occurs, or when dilatation of the aortic root causes severe aortic regurgitation. Resection of the aneurysmal segment with replacement by a synthetic graft, with aortic valve replacement if necessary, is the definitive treatment of ascending thoracic aortic aneurysms. Prophylactic resection is often indicated in patients with Marfan syndrome when the aneurysm is 5.5 cm or larger in diameter because of an increased propensity for rupture in these patients. Aneurysms involving the descending thoracic aorta are usually managed conservatively because surgical removal is a formidable task; an operation is frequently indicated, however, if the aneurysm is larger than 8–10 cm in size, is progressively enlarging or is causing symptoms.

Aneurysm of the Abdominal Aorta

Etiology Aneurysms occur much more often in the abdominal aorta than in the thoracic aorta. Abdominal aneurysms are nearly always located distal to the renal arteries. Although they are usually considered to be atherosclerotic lesions, it has been suggested that a genetically determined generalised arteriopathy may be responsible for the lesion. This view is strengthened by the observations that abdominal aneurysms are more common in men, exhibit a familial clustering and are associated with other vascular aneurysms.

Clinical features Abdominal aneurysms develop gradually. Clinically, the aneurysm appears as a pulsating abdominal mass and can usually be detected on physical examination before any symptoms develop. Abdominal aortic aneurysms typically expand at a rate of approximately 0.2 cm per year. With progressive enlargement, the aneurysm can cause abdominal pain and can rupture. Occasionally the initiating event is rupture of the aneurysm without any prior warning.

Investigations Non-invasive techniques (ultrasound, CT, MRI) are reliable for detecting abdominal aortic aneurysms and for evaluating their size. These techniques have replaced aortic angiography. Ultrasonography identifies virtually all lesions and accurately indicates their size in most instances. CT and MRI have the advantage that they can also demonstrate any evidence of rupture and can define any involvement of the renal artery.

Treatment Patients with abdominal aneurysms that are smaller than 5 cm in diameter can be followed up at six-month intervals with serial ultrasonographic studies. Elective surgery is advisable in the absence of other medical contraindications, for all abdominal aneurysms larger than about 5 cm in diameter since the mortality of emergency surgery for a ruptured aneurysm (25–50%) is tenfold higher than that of elective surgery (2–5%). Resection of abdominal aneurysms and replacement with a prosthetic graft is the procedure of choice.

AORTIC DISSECTION

Aortic dissection is a condition in which a tear in the intima of the aorta is followed by entry of blood into the vessel wall in the plane between the tunica media and the tunica intima.

Etiology Ascending aortic dissection usually results from associated hypertension or any connective tissue disorder which weakens the aortic wall. Aortic coarctation, the bicuspid aortic valve, Marfan syndrome and Turner syndrome are less frequent causes of aortic dissection. Distal aortic dissections are related more often to atherosclerosis.

Pathophysiology Aortic medial degeneration is present in most pathology specimens of aortic dissection but it is not a prerequisite for the

development of dissection. The initial pathologic lesion is a transverse intimal tear which separates the inner layer as a 'flap' from the rest of the aorta. This process divides the aorta into a central *true lumen* and a surrounding *false lumen*. The blood in the wall of the aorta may reenter the true lumen through secondary tears called *'reentry'* tears. The clinical picture, outcome and treatment strategies are determined by whether or not the ascending aorta is involved. Aortic dissections, therefore, are classified into Type A dissections which involve the ascending aorta and Type B dissections which involve any other portion of the aorta.[1] Two-thirds of cases involve the ascending aorta. Ascending aortic dissections are frequently associated with aortic regurgitation, rupture of the false lumen into the pericardium (and consequent hemopericardium with tamponade), and coronary artery occlusion. The dissection flap can cause ischemia of various viscera by occluding the origin of aortic branches supplying these organs (Fig 12.71).

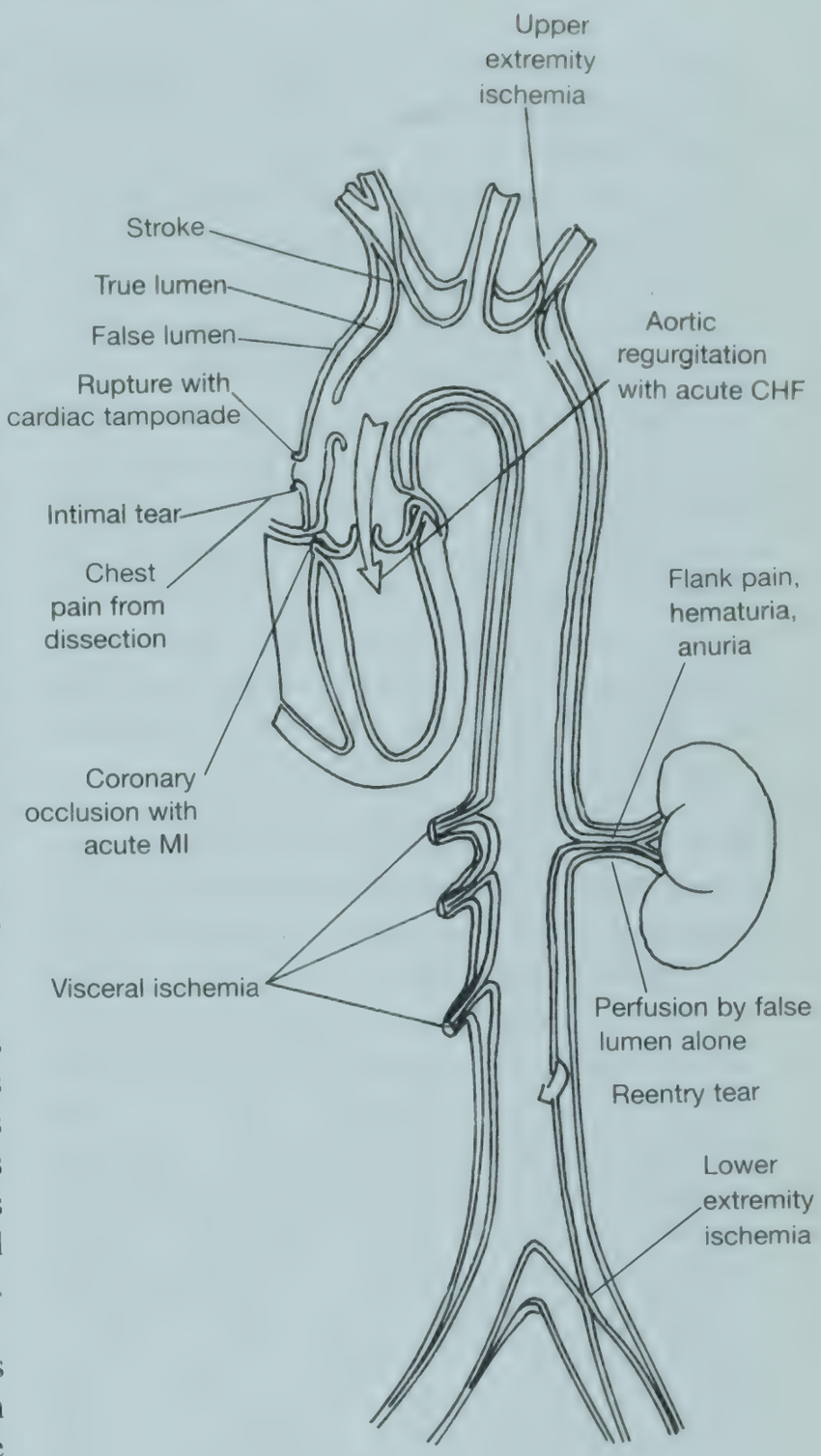


Fig 12.71 Ascending aortic dissection (pathophysiology)

Clinical features Aortic dissection occurs most often in the fifth to seventh decades of life. Men are affected twice as often as women. Patients presenting within 14 days of initial symptoms are categorised as *acute dissections* and those presenting beyond this period are labelled as *chronic dissections*. Such a classification has prognostic value.

Chest pain which is tearing in character and is located anteriorly or in the interscapular region is the commonest symptom. Typically, the patient appears to be in 'shock' but is found to be hypertensive on examination. A precordial murmur of aortic regurgitation may be evident in Type A dissections. Disruption of major aortic branches may be associated with a variety of clinical symptoms and signs. A difference in palpable upper limb pulses or blood pressures, syncope or stroke due to interference with cerebral circulation are important clues to the diagnosis of aortic dissection. In dissections extending to the descending thoracic aorta, interruption of blood supply to the spinal cord can result in paraplegia.

[1] An alternative classification labels Type I dissections as arising in the ascending aorta and extending distal to the brachiocephalic artery. Type II dissections are those confined to the ascending aorta, and Type III dissections as arising in the descending thoracic distal to the origin of the left subclavian artery.

Diagnosis The ECG may be helpful by failing to show evidence of myocardial infarction in a patient suspected to have the same. The chest radiograph is often helpful if it reveals a widened mediastinum or a left pleural effusion.

The definitive diagnostic tests for dissection are a transesophageal echocardiogram (TEE), computerised tomography (CT), MRI scan of the chest or aortography. Each of these tests is fairly sensitive and specific in substantiating a clinical diagnosis of aortic dissection and the choice may be guided by availability and urgency; TEE and CT scans are preferable for acute dissections and MRI for chronic dissections. All these tests demonstrate the presence of an aorta with the two lumens separated by an intimal flap.

Treatment All acute ascending aortic dissections are treated surgically. Chronic ascending aortic dissections and dissections of the descending thoracic aorta can be managed medically. Surgery may be indicated in distal dissections if there is evidence of leakage, extension or vital organ (bowel or renal) ischemia. Even patients with acute ascending aortic dissection require initial stabilisation with medical treatment while awaiting surgery. Medical treatment consists of antihypertensive agents that reduce aortic wall stress; a combination of sodium nitroprusside (25–50 micrograms/min, increased to upto 300 micrograms/min) and β-blockade (i.v. propranolol 0.5 mg followed by increments of 1–2 mg q 5 min till the heart rate slows to 60–70 beats per min) is ideal. Surgery consists of excision of the dissected portion and replacement with a synthetic graft.

Prognosis Untreated acute aortic dissection is associated with a 75 per cent mortality in 2 weeks. The majority of deaths occur during the initial 48 hours.

NON-SPECIFIC AORTOARTERITIS (TAKAYASU'S DISEASE,[1] PULSELESS DISEASE)

Aortoarteritis is a chronic inflammatory disease of unknown origin characterised by narrowing of the aorta and one or more of its branches.

Epidemiology Aortoarteritis is more common in Asian countries. Women are affected more often than men in a ratio of 8:1. The age of onset is typically less than 40 years.

Etiology and pathology It is thought that the disease has an autoimmune basis; antibodies against aortic tissue have been described but their role is uncertain. An association with HLA Bw52 and DR12 antigens has been reported. The commonest sites of the aorta that are involved are the origin of the subclavian arteries and the infrarenal segment of the abdominal aorta. Other arch vessels are also frequently narrowed by the disease process. Pathologically, vascular inflammation is usually confined to the media and the adventitia, with thickening of the intima occurring at the end stage. Aneurysmal dilatation of diseased segments is a less common feature. Four types of aortoarteritis have been described based on the distribution of vascular lesions: Type 1 involves the aortic arch and its branches, Type 2 involves the descending thoracic aorta and abdominal aorta, Type 3 involves features of Types 1 and 2 and Type 4 represents pulmonary artery involvement with any of the previous types.

Clinical features In about half the patients, aortoarteritis begins as a systemic illness (prepulseless stage) characterised by fever, malaise, arthralgia and fatigue. The prodromal phase usually lasts upto 18–20 months. This phase blends insidiously into the chronic phase

[1] Named after the Japanese ophthalmologist M. Takayasu who described the ocular findings in this condition in a young woman in 1908.

characterised by inflammatory obliterative changes of the lumina of the aorta and its major branches. The presenting symptoms are usually those of arterial insufficiency. The involvement of the external and internal carotid arteries is associated with symptoms such as claudication of the jaw muscles, visual disturbances, syncope or even transient ischemic attacks. Vertebral artery involvement is associated with episodes of dizziness and light-headedness. The involvement of the renal arteries is associated with renovascular hypertension. Cardiac failure is frequent and may result from uncontrolled hypertension, coronary involvement or, rarely, aortic regurgitation. Indeed, cardiac failure is the commonest cause of death in these individuals. Aneurysmal dilatation of involved branches has been well-recognised (upto 20%), as is pulmonary hypertension consequent to involvement of the pulmonary arteries.

The physical examination reveals absent or diminished upper limb pulses and hypertension in the lower extremities: hence the term 'reversed coarctation'. Bruits may be heard over involved arteries and are important clues to the diagnosis. Examination of the retina may show changes secondary to hypertension or, less commonly, the more specific feature of wreath-like arteriovenous anastomoses.

Diagnosis A definitive diagnosis of aortoarteritis is made with angiographic visualisation of the aorta and its branches with contrast aortography or by intraarterial digital subtraction angiography. The erythrocyte sedimentation rate is frequently elevated in the acute phase of the disease.

Treatment There is no approved treatment for reversing or arresting the progression of aortoarteritis. Hypertension should be treated with antihypertensive agents; care should be taken to exclude bilateral renal artery stenosis prior to the use of angiotensin converting enzyme inhibitors. Balloon angioplasty has a limited role for treating localised stenoses of renal arteries. Surgery has been used for the chronic phase of the disease if the symptoms are disabling, and consists of excision of large arterial aneurysms and bypassing of obstructions. There are initial reports that have demonstrated the beneficial effect of corticosteroids and cytotoxic agents in upto 75 per cent of patients in the acute phase of the disease.

Prognosis The major complications of aortoarteritis include stroke, heart failure and severe hypertension. These complications are markers of an adverse outcome (5-year survival 60%). In the absence of complications, the 5-year survival has been reported to be as high as 95 per cent.

PERIPHERAL VASCULAR DISEASE

Chronic Peripheral Vascular Disease

Etiology Chronic peripheral arterial disease most commonly affects the lower extremities and is most often atherosclerotic in origin. The preferential affliction of the lower extremities stems from the greater preponderance of atherosclerotic lesions in the lower limb arteries, a greater circulatory demand of the lower extremities and the relative abundance of arterial supply to the upper extremities.

The major cause of chronic arterial occlusive disease is atherosclerosis. Hypertension, diabetes mellitus, smoking and hyperlipidemia are risk factors for atherosclerotic arterial disease in the lower limb arteries, as in the coronary arteries. The prevalence of arterial disease increases with age from less than 3 per cent in those less than 60 years to over 20 per cent in those above 75 year. Atherosclerotic lesions most often occur at arterial bifurcations, at the sites of branching and in the adductor canal (where the femoral artery passes through a muscle sling). Collateral vessels usually develop to reduce the effects of the arterial stenoses.

Clinical features The classical symptom of lower limb arterial occlusion is *'claudication'*.[1] Claudication is the sense of tightness, 'crampy discomfort' occurring after exertion, which is relieved dramatically with rest and is related to the speed of walking and the incline of the path. Typically, walking for a predictable distance (claudication distance) brings on the discomfort. The location of the discomfort can help to localise the site of arterial obstruction. Instep claudication signifies disease distal to the popliteal artery, calf claudication identifies popliteal or femoral obstruction, thigh claudication indicates iliac obstruction and gluteal claudication denotes aortoiliac disease. Aortoiliac disease may be associated with impotence in men. As the severity of arterial obstruction progresses, rest pain may supervene as the basal perfusion demands of the extremity are not met. This is characterised by a burning sensation in the toes and feet especially on assuming a supine position. Rest pain may be relieved by dependency due to gravity-dependent augmentation of arterial flow. Impotence along with thigh claudication often indicates disease of the aortic bifurcation. With further worsening of arterial obstruction, rest pain culminates in skin changes. Atrophic, hairless skin, dependent rubor with pallor on slight elevation of the limb are associated with advanced ischemia. Pregangrene begins as areas of discolouration that lack sensation.

Diagnosis A careful palpation of the lower extremity pulses is important to determine the presence and extent of arterial insufficiency. In aortoiliac disease, femoral pulses are typically absent. In femoropopliteal disease, all the pulses below the femoral artery are absent. The presence of femoral and popliteal pulses along with absent foot pulses denotes small vessel disease (often due to diabetes mellitus or Buerger's disease). If claudication is present but lower extremity pulses are intact, the possibility of *neurospinous claudication* (lumbar canal stenosis) must be considered. Resting pallor of extremities indicates severe ischemia. A simple test is to elevate the leg upto 45 degrees with the patient supine. The patient then shifts to the sitting position and the colour of the plantar aspect of the foot is observed; a delay in return of normal colour of the sole (greater than 20–30 seconds) indicates inadequate development of collaterals. The measurement of systolic blood pressure at the ankle and comparing it with the brachial blood pressure (*ankle-brachial index*) is another useful test for evaluating lower extremity arterial insufficiency. The normal ratio is greater than 1.10; values below 0.9 indicate arterial insufficiency and values less than 0.3 indicate impending tissue necrosis with risk of gangrene. An absolute level of ankle systolic pressure less than 55 mmHg signifies severe limb ischemia. Doppler ultrasound is also used for non-invasive imaging of lower limb arteries.

Treatment Mild to moderate claudication responds favourably to a programme of smoking cessation, exercise training and control of other risk factors for arterial disease. Vasodilators are commonly prescribed although definitive proof of efficacy is lacking. Pentoxyfylline 400 mg t.i.d. is helpful in select cases. Severe claudication or rest pain necessitates further investigation to document the location and extent of vascular stenoses with angiography. Definitive treatment consists of revascularisation procedures. Short non-calcific segmental iliac lesions can be treated effectively with percutaneous transluminal angioplasty. Long segments of disease are treated with a bypass graft that diverts blood from the proximal part to the part of the vessel distal to the stenoses using an autogenous vein or a woven Dacron graft. Lumbar sympathectomy is reserved for patients with incapacitating claudication who are not candidates for surgery. Amputation may occasionally be required for progressive gangrene, unrelenting rest pain or for uncontrolled infection.

[1] From the latin word *claudicare*, meaning 'to limp'

Prognosis Detection of lower extremity arterial disease is of prognostic importance as it provides rapid assessment of atherosclerosis elsewhere in the body. It also identifies individuals with a mortality four to five times that of individuals without arterial disease of the lower extremities. In about 25 per cent of patients, arterial disease of lower extremities is progressive leading to loss of mobility, gangrene and amputation.

Acute Lower Limb Ischemia

Etiology The two principal processes that lead to acute ischemia of the lower extremities are arterial embolism and arterial thrombosis. Arterial embolism is most often secondary to a cardiac cause; atrial fibrillation secondary to rheumatic or coronary artery disease is a very common predisposing condition. Emboli tend to lodge at the bifurcation of the major arteries; more than 50 per cent of emboli involve the aortic bifurcation and the lower limb vessels. Acute arterial thrombosis generally occurs in a vessel with atherosclerotic changes and a markedly narrowed lumen.

Clinical features The clinical features of acute limb ischemia are similar irrespective of the underlying etiology. The patient complains of sudden severe *pain*[1] in the extremities alongwith numbness and *paresthesia.* The affected limb appears *pale,* feels cold and the superficial veins are collapsed. As limb ischemia continues, *paralysis* of the limb results. Clues to the possibility of an embolism include the presence of rhythm disturbances (atrial fibrillation), rheumatic valve disease or coronary disease with ventricular dyskinesia. A history of intermittent claudication or the presence of chronic ischemic disease of the opposite limb (bruits, absent/diminished pulses) favours the possibility of in situ thrombosis.

[1] The four Ps of acute limb ischemia are pain, pallor, paresthesia and paralysis.

Diagnosis and treatment Arteriography is the procedure of choice for investigating an acutely ischemic limb. A contrast study remains the gold standard although MR angiography has supplanted this in some centres. Differentiation of an embolism from thrombosis is essential as the treatment approach is different for the two conditions. An embolus is treated with embolectomy. The embolus is extracted by means of a balloon-tipped catheter (Fogarty catheter) inserted through an arteriotomy made under local anesthesia. This should be done *within 12 hours (ideally within 4–6 hours).* A non-operative approach is preferable for a thrombotic occlusion as the underlying diseased segment tends to be long (making surgery difficult) and also because of the likelihood of greater collateral circulation. Thrombolytic therapy with streptokinase has been utilised for the treatment of acute arterial thrombosis provided there is no contraindication. Successful lysis is achieved in up to 50–80 per cent of cases. Thrombolytic therapy must be followed up with evaluation for treating the underlying atherosclerotic segment with revascularisation procedures. In either case, anticoagulation with heparin is initiated with a switch to oral anticoagulants after the acute episode resolves. If atrial fibrillation is the precursor, cardioversion (pharmacologic or electrical) should be considered as a therapeutic option.

Prognosis Acute limb ischemia is a threat not only to the involved limb but to the life of the patient (mortality rates vary from 10–30%).

Raynaud's Phenomenon and Disease

Both these disorders are characterised by intermittent attacks of pallor or cyanosis affecting the fingers and toes. The term Raynaud's disease is used when the disorder is idiopathic. When the disorder occurs secondary to systemic disease, the term Raynaud's phenomenon is used.

Etiology Raynaud's disease is believed to be related to hyperresponsiveness of the digital arteries to vasospastic stimuli such as cold; hyperactivity of the digital sympathetic supply has been implicated. Raynaud's phenomenon may be secondary to other autoimmune disorders (systemic sclerosis, systemic lupus erythematosus, mixed connective tissue disease), thoracic outlet syndromes (cervical rib), cryoglobulinemia (idiopathic or secondary to hyperglobulinemic states such as multiple myeloma) or related to drugs (beta-blockers, ergot drugs, anticancer drugs bleomycin and vincristine administered in combination).

Clinical features Raynaud's disease occurs more often in young women, and as a rule is symmetric. The disorder is characterised by episodes of intense pallor involving the fingers (and occasionally the toes) precipitated by cold or emotional upsets. Pallor is accompanied by pain and numbness of affected fingers. Pallor is followed by cyanosis which is followed by redness (rubor) as the attack subsides. Attacks usually subside with return to a warm environment or by immersing fingers in warm water. In rare cases, the condition may progress to digital atrophy and gangrenous ulceration of the fingertips.

When the condition occurs in a man, is unilateral or affects only 1–2 fingers, Raynaud's phenomenon secondary to a systemic process should be strongly suspected.

Diagnosis When symptoms persist for more than three years without the appearance of a systemic disease, Raynaud's disease may be diagnosed. This is important because in several autoimmune disorders the phenomenon may precede other clinical manifestations. Peripheral pulses are normal in Raynaud's disease; this enables a distinction from other peripheral vascular diseases. The diagnosis is clinical and no single laboratory abnormality is diagnostic. In every patient, a careful search for a secondary cause must be made. Ergot poisoning must also be considered in the differential diagnosis.

Treatment The mainstay of treatment is protecting the fingers from cold exposure. Beta-blocking drugs and smoking should be stopped. Vasodilators are generally of little benefit, although low-dose nifedipine (10 mg t.i.d.) has been reported to be useful. Sympathectomy may be indicated if the attacks are frequent, disabling and if trophic digital changes have developed; it provides temporary relief and subsequent attacks (if they occur) are milder.

Prognosis Raynaud's disease is benign with very few patients reporting trophic digital changes. The prognosis of Raynaud's phenomenon is related to the underlying condition.

Thromboangitis Obliterans (Buerger's disease)

Buerger's disease is a disease of unknown etiology characterised by an episodic inflammatory process involving the arteries and veins of the extremities. A hypersensitivity to nicotine has been invoked as a causative mechanism.

Pathogenesis and pathology The symptoms of the disease are related to chronic segmental inflammatory and thrombotic arteritis and venulitis of limb blood vessels. The plantar and digital blood vessels of the feet are most often affected. Arterial segments undergo occlusion and recanalisation successively until the lumen is obliterated. At this stage chronic ischemia gives way to impending gangrene.

Clinical features Buerger's disease predominantly affects young men below 40 years who smoke. There may be a history of episodes of superficial thrombophlebitis characterised by small red tender cords usually involving the saphenous veins. Intermittent claudication is frequent and involves the instep of the foot and the palm of the hands. The proximal arterial

pulses are typically intact though diminution of pulsations of the dorsalis pedis, posterior tibial, radial or ulnar arteries is frequent. The age of the patient and the preservation of proximal pulses differentiates these patients from those with atherosclerotic peripheral vascular disease. Chronic ischemia is associated with rest pains as well as with trophic changes affecting the skin and nail of the distal part of extremities. Initially, the development of collaterals preserves blood supply, but as these get occluded by the inflammatory process, rest pains and pregangrene may supervene.

Treatment Cessation of smoking is the most important step. If the symptoms are severe and limit work capacity, sympathectomy has been advocated. Gangrenous portions of the extremities require amputation.

Prognosis The prognosis is excellent if the subject stops smoking.

Other Peripheral Vascular Disorders

Acrocyanosis is a condition affecting men and women alike, characterised by an onset of chronic coldness and cyanotic discolouration of fingers and toes without associated trophic changes or pain, in the teenage years. This is due to the combination of digital arteriolar constriction alongwith dilatation of the venous plexus of the skin; the slow circulation leads to excessive deoxygenation of blood and hence gives the cyanotic appearance.

Livedo reticularis is an uncommon vasospastic disorder of young women characterised by mottled areas of discolouration of extremities exhibiting a typical 'fish net' appearance with peripheral cyanotic areas around a central pale core. It is most frequent on the thighs and the forearms. It may be idiopathic or secondary to other conditions such as polyarteritis nodosa, malignant neoplasms, or atherosclerotic microemboli.

KEY CONCEPTS

Ascending aortic aneurysm

- Twenty-five per cent of aortic aneurysms arise from the ascending thoracic aorta. The predisposing conditions include Marfan syndrome and syphilitic aortitis.
- The symptoms are related to compression of mediastinal structures (more common with arch aneurysms): cough, wheezing, dysphagia, hoarseness, Horner syndrome and pain radiating to the back.
- Large ascending aortic aneurysms can be easily seen on the chest X-ray. A CT or an MRI scan is preferred for evaluating the size and extent of the aneurysm.
- Surgical repair is recommended for most aneurysms ≥7 cm; in Marfan syndrome, surgery is recommended when the aortic size is ≥5.5 cm.

Abdominal aortic aneurysm

- Seventy-five per cent of aortic aneurysms arise in the abdominal aorta and a majority are infrarenal. Abdominal aortic aneurysms may be related to atherosclerosis, hypertension, smoking or a familial tendency.
- Abdominal aortic aneurysms may be saccular (localised outpouching) or fusiform (circumferential widening). The aneurysm frequently involves the iliac vessels and often contains laminated thrombi.
- Most often they are discovered incidentally on an abdominal sonogram obtained for some other purpose. Occasionally, patients may complain of a steady lumbosacral pain. The most common physical finding is that of a pulsatile abdominal mass.
- Ultrasonography is a good screening test for abdominal aortic aneurysms. A CT or an MRI scan yields better definition of the size and the extent.
- Generally, abdominal aortic aneurysms grow at a rate of 0.2 cm/year. The risk of rupture increases when the aneurysm is ≥6 cm. Rupture of an abdominal aortic aneurysm is a catastrophic event.
- For aneurysms <6 cm, treatment consists of controlling blood pressure and monitoring the rate of increase in size with serial sonographic examinations. Elective surgical repair is recommended for all abdominal aortic aneurysms once they are 6 cm in size.

Aortic dissection

- In aortic dissection, blood enters the wall of the aorta through an intimal tear and strips the media from the adventitia. The predisposing conditions include hypertension, Marfan syndrome and atherosclerosis.
- Ascending aortic dissection (Type A) presents with crushing chest pain which may be associated with focal neurologic deficit (stroke or TIA), syncope or cardiac tamponade. Descending aortic dissection (Type B) presents with severe interscapular pain.
- Findings on physical examination that are suggestive of aortic dissection include asymmetric carotid (or peripheral) pulses and a murmur of aortic regurgitation.
- The ECG is usually normal unless there is coronary artery involvement (ascending aortic dissections). The chest X-ray may reveal a widened mediastinum. The diagnostic investigations of choice include a TEE, a CT scan and an MRI scan. TEE and CT are preferable for acute aortic dissection while an MRI scan may be used in chronic aortic dissection.
- Treatment measures include lowering the elevated blood pressure with beta-blockers and sodium nitroprusside. Surgery is recommended for acute Type A dissections. Medical management is preferred for Type B dissections and for chronic dissections.

Non-specific aortoarteritis (Takayasu's disease)

- This is a disease of unknown etiology characterised by chronic inflammatory aortitis that has a predilection for the origin of the subclavian arteries and the abdominal aorta. Women are affected more often than men and the disease is more common in Asia and southeast Asia.
- There is an initial systemic illness with prominent fever and arthralgia followed by a chronic phase characterised by an obliterative arteritis. The chronic phase is characterised by pulse deficits, hypertension, claudication and CHF. Prominent findings on examination (besides hypertension) include absent pulses in the upper extremities *(reverse coarctation)* and bruits over affected vessels. Aneurysmal dilatation of aortic segments may be seen.
- Treatment measures for the acute phase of the disease include steroids with a possible adjunctive role of immunosuppressive agents. In the chronic phase of the disease, treatment methods include control of hypertension, angioplasty for localised obstruction associated with visceral ischemia (as in renal artery stenosis), and resection of large aneurysms.

12.13 Pulmonary hypertension, cor pulmonale and acute pulmonary embolism

Pulmonary Hypertension

Pulmonary arterial hypertension is defined as the presence of elevated pulmonary arterial pressure, usually a systolic pressure above 30 mmHg and a mean pressure above 25mmHg; normally, pulmonary artery pressures are 18–25 mmHg systolic, 10 mmHg diastolic and 15 mmHg mean. Pulmonary hypertension is considered severe when pulmonary arterial pressure is more than 75 per cent of the systemic arterial pressure.

Etiology Pulmonary arterial hypertension may result from a variety of disorders or may be idiopathic in which case it is called 'primary pulmonary hypertension'. The causes of pulmonary arterial hypertension are shown in Table 12.37. The commonest cause of pulmonary arterial hypertension is left atrial hypertension due to any cause. Mitral valve diseases and left ventricular failure are important causes under this category. Pulmonary hypertension due to parenchymal pulmonary disease is referred to as cor pulmonale although there are more components to this entity than just pulmonary arterial hypertension and this will be discussed later. Pulmonary arterial hypertension is also a component of Eisenmenger syndrome (reversed shunt condition with dominant right to left shunting).

Pathophysiology, pathology and clinical features The key component of pulmonary arterial hypertension is an increase in pulmonary vascular resistance. The three primary mechanisms of an elevated pulmonary vascular resistance are 1) loss of pulmonary blood vessels, 2) obstruction of pulmonary blood vessels, and 3) narrowing of pulmonary blood vessels. Loss of pulmonary blood vessels is seen in patients with interstitial pulmonary fibrosis and other parenchymal lung diseases, as well as in patients with surgical resection of segments of the lung. Obstruction to pulmonary vessels is seen in both

Table 12.37 Causes of pulmonary arterial hypertension

1. **Primary pulmonary hypertension**
2. **Pulmonary veno-occlusive disease**
3. **Cardiac disease**
   - Mitral valve disease
   - Left atrial myxoma
   - Left ventricular failure
   - Congenital heart disease
4. **Cor pulmonale**
   - Obstructive airways disease
   - Diseases of the lung parenchyma
     - Alveolar
     - Interstitial
   - Pulmonary vascular disease
     - Collagen vascular disease
     - Thromboembolic disease
   - Neuromuscular disease
     - Abnormal chest bellows
     - Disordered respiratory control mechanisms

acute and chronic pulmonary thromboembolic disease. Narrowing of the pulmonary vessels may be anatomic, such as a consequence of chronic hypoxia and chronic obstructive airway disease, or vasoconstrictive as in acute hypoxia.

The typical pathological features of pulmonary arterial hypertension include medial hypertrophy, concentric intimal fibrosis and the *plexiform lesion.* Plexogenic pulmonary arteriopathy is usually seen with primary pulmonary hypertension or in the Eisenmenger syndrome and the hallmark is the plexiform lesion which refers to dilated thin-walled side branches of the pulmonary arterioles with endothelial proliferation. Apart from these anatomic changes, functional changes in the pulmonary vasculature have also been described in primary pulmonary hypertension and may be important in the genesis of the disorder. In primary pulmonary hypertension, the pulmonary arterioles seem to have a defect in the endothelium-derived relaxation factor.

Signs and symptoms These may vary depending on the underlying disorders, yet there are several common features. The typical complaints are of dyspnea, fatiguability and atypical chest pain. With severe, longstanding pulmonary hypertension, symptoms of right heart failure may supervene with prominent peripheral edema and ascites. Syncope can occur on occasion. When the pulmonary hypertension is secondary to left atrial hypertension, symptoms of pulmonary venous congestion are predominant and include orthopnea, dyspnea on exertion and paroxysmal nocturnal dyspnea. Patients with the Eisenmenger syndrome may give a past history of recurrent chest infections in childhood. A history of smoking and frequent episodes of bronchitis are essential for the diagnosis of underlying chronic obstructive airway disease. Due to right ventricular hypertrophy a palpable second sound in the second left intercostal space (which is the palpable pulmonic component) and a palpable thrill of tricuspid regurgitation may be present. On auscultation, the second heart sound varies in splitting depending on the underlying etiology but the pulmonic component is usually very loud. In primary pulmonary hypertension and pulmonary hypertension due to left atrial hypertension, the second heart sound is closely split. In the Eisenmenger syndrome, the splitting of the second heart sound depends on the location of the shunt. Thus in an Eisenmenger ASD, the second sound is wide, fixed split, in a VSD with reversal of shunt, the second heart sound is single, and in an Eisenmerger PDA the second heart sound is usually normally split. A right ventricular fourth heart sound is usually present and a systolic ejection click can be heard over the dilated pulmonary artery. When right ventricular failure supervenes, a right ventricular third heart sound and the systolic murmur of tricuspid regurgitation can be heard. A high-pitched early diastolic murmur of pulmonary regurgitation may be heard in cases with severe pulmonary arterial hypertension. The typical appearance on a chest X-ray is of dilated pulmonary vessels at the hilum with peripheral pruning. The underlying disorder will affect the appearance on the chest X-ray. Thus, a calcified mitral valve or an enlarged left atrial appendage suggests underlying mitral stenosis. Prominent end-on pulmonary vessels suggest a preexisting shunt lesion and an Eisenmenger syndrome. The right atrium and the right ventricle may appear enlarged on the chest X-ray. The electrocardiogram shows evidence of right axis deviation, tall P waves (P pulmonale), and tall R waves in V_1 and V_2. Two-dimensional echocardiography may aid in delineating the underlying cause of pulmonary hypertension. The left ventricular contractility can be assessed as also the mitral valve. An underlying shunt at the atrial, ventricular or the ductus level can be detected with Doppler echocardiography. In the presence of tricuspid regurgitation, an estimate of pulmonary arterial pressure can be obtained non-invasively with Doppler echocardiography. Cardiac catheterisation establishes the severity

of pulmonary arterial hypertension, helps to determine its response to vasodilator drugs, and helps in ruling out intracardiac shunts. The presence of a normal pulmonary capillary blood pressure and the absence of any shunt suggests that the underlying etiology may be primary pulmonary hypertension provided underlying pulmonary parenchymal disease is absent.

Natural history The prognosis in pulmonary arterial hypertension depends on the underlying etiology. The prognosis in primary pulmonary hypertension is notably poor with a 5-year survival of only 20 per cent. The prognosis is excellent when there is a treatable cause like a stenotic mitral valve, an operable shunt lesion or constrictive pericarditis. The prognosis in patients with chronic obstructive airway disease depends on the severity of the underlying lung disease.

Treatment The treatment of pulmonary arterial hypertension depends on the underlying etiology. Thus, surgical correction for mitral valve disease or myocardial revascularisation (where the left ventricular dysfunction is secondary to coronary artery disease) will result in a rapid reduction of pulmonary arterial hypertension. If patients with left-to-right intracardiac shunts are operated before irreversible pathological changes develop in the pulmonary vasculature then the pulmonary hypertension is reversible in these patients. Chronic oxygen therapy has been shown to improve pulmonary arterial hypertension due to chronic obstructive lung disease. Anticoagulant therapy has been shown to improve the survival of patients in primary pulmonary hypertension. These patients have been treated with a number of vasodilator drugs which may reduce the level of pulmonary pressures. Agents which have been used include sublingual isoproterenol, calcium channel blockers like nifedipine, converting enzyme inhibitors like captopril, and direct vasodilators like hydralazine and tolazoline. When right ventricular failure develops, it should be treated with digoxin and diuretics. When pulmonary arterial hypertension is irreversible as in the Eisenmenger syndrome, the only potential form of treatment may be a combined heart and lung transplantation. Currently this form of therapy is extremely expensive and is not available in India.

Cor Pulmonale

Cor pulmonale has been defined by the World Health Organisation as 'right ventricular enlargement resulting from disorders which affect either the structure or the function of the lungs'. It is important to note in this definition that clinical evidence of right ventricular failure is not essential for the diagnosis of cor pulmonale although it tends to be the main presenting feature in this disorder.

Etiology and pathophysiology The causes of cor pulmonale have been shown in Table 12.37. The most common cause of cor pulmonale in India is chronic obstructive airway disease. The other important causes in order of priority include suppurative pulmonary disease such as bronchiectasis, pulmonary tuberculosis and the pneumoconioses. Cor pulmonale is seen in patients with chronic obstructive lung disease who have dominant chronic bronchitis, that is, who are known as the blue bloaters. The *Pickwickian syndrome* refers to the syndrome of obesity, somnolence, and cor pulmonale. The *sleep apnea syndrome* refers to a condition where the patients have repetitive apnea during sleep, with periods of hypoxemia and hypercapnia alternating with periods of normal breathing.

The episodes of apnea result in hypoxia which in turn results in progressive pulmonary vasoconstriction and consequent pulmonary arterial hypertension during sleep. Some people with this disorder have obstruction of the upper airways *(obstructive sleep apnea)* and other patients have an abnormal ventilatory drive due to reduced sensitivity of the central respiratory

centre *(central sleep apnea)*. The symptoms and signs of cor pulmonale are those of pulmonary arterial hypertension and right ventricular failure. There will be physical signs depending on the underlying condition. Thus chronic obstructive airway disease with cor pulmonale may be characterised by prominent cyanosis, and signs of respiratory failure. Bronchiectasis will be suggested by the presence of localised coarse crepitations. Obstructive sleep apnea may be suggested by the presence of enlarged tonsils and adenoids. Important investigations must include the pulmonary function tests and blood gas analysis to document the severity of hypoxemia and the severity of pulmonary impairment.

Treatment The treatment of cor pulmonale is aimed at treatment of the underlying pulmonary problem, reducing pulmonary hypertension and treating associated right ventricular failure. Thus, chronic obstructive lung disease is treated with bronchodilators, the cessation of smoking and supplemental oxygen. The administration of supplemental oxygen has now has been shown to improve survival in patients with cor pulmonale due to chronic obstructive airway disease. Usually 12–15 hours of daily oxygen therapy at about two litres per minute are required and may be administered especially in patients during the night when the periods of hypoxemia tend to be more frequent. Diuretics can be used for treating right ventricular failure especially in patients with peripheral edema. Digitalis has also been used for the treatment of right ventricular failure but must be used with care in these patients as they are at an increased risk for digitalis toxicity. A number of vasodilator drugs have been tried in cor pulmonale but generally have the disadvantage of causing systemic hypotension. Patients with the Pickwickian syndrome are treated with weight reduction and progesterone. The obstructive sleep apnea syndromes have been treated with weight reduction (when the patients are obese), avoidance of sleeping in the supine posture, continuous positive airway pressure of the nose during sleep, and rarely, tracheostomy in the few patients with severe obstructive sleep apnea in whom all the other treatment measures have failed. Therapy for central sleep apnea syndrome include management of the underlying hypoventilation disorder, nocturnal supplemental oxygen administration if hypoxemia is significant, and the avoidance of any drugs that depress the ventilatory drive (such as sedatives or antihistamines).

Pulmonary Thromboembolism

Definition and epidemiology Pulmonary thromboembolism refers to complete or partial obstruction of the pulmonary arterial bloodflow by a clot or thrombus lodged in the pulmonary circulation. Evidence of recent or past pulmonary embolism is detected in upto 30 per cent of routine autopsies. An antemortem diagnosis of pulmonary embolism however is made only in a third of these cases. This suggests that many pulmonary thromboemboli may be clinically silent or may not be suspected clinically. Autospy data also suggests that less than 10 per cent of all pulmonary emboli result in death.

Etiopathogenesis More than 95 per cent of pulmonary thromboemboli arise from thrombi in the deep venous system in the lower extremities. The popliteal veins and the larger leg veins above are the most common sources of pulmonary emboli. In situ thrombosis in the pulmonary arterial circulation is rare. A few pulmonary emboli do reach the pulmonary circulation from thrombi located in the right-sided cardiac chambers.

Pulmonary embolism should therefore be viewed as a complication of deep venous thrombosis in the lower extremity veins. These thrombi develop in the region of a venous valve in the leg veins beginning as a predominant platelet thrombus *(white thrombus)* followed by further deposition of fibrin *(red thrombus)*.

The natural history of these thrombi in the lower extremity veins is either natural fibrinolysis with a resolution or organisation of the thrombi. The venous valves are often rendered incompetent by this process and luminal narrowing of the veins may be found. During the first few days before these processes of fibrinolysis or of organisation can begin, there is maximum embolic risk of the thrombus reaching the pulmonary arterial circulation. The conditions which predispose to a high risk of deep venous thrombosis in the lower extremities include prolonged bedrest, obesity, chronic deep venous insufficiency of the legs, fractures or other injuries of the lower extremities, left and right ventricular failure, any surgical procedure requiring prolonged general anesthesia, the postpartum period and the use of drugs like estrogens. Rare conditions which together are classified as *hypercoagulable states* may also, on occasion, predispose to the formation of thrombi in the deep veins of the legs. These hypercoagulable states include deficiencies of essential components of the clotting system like antithrombin-3, protein C, protein S, and the presence of antiphospholipid antibodies in serum.

Pathophysiology When a clot is lodged in the pulmonary circulation, it produces an area which is ventilated but not perfused, that is, wasted ventilation. Within 3–4 hours of cessation of capillary blood flow to the alveoli, there is loss of alveolar surfactant. Frank atelectasis can be detected 24–48 hours after interruption of bloodflow and is a result of loss of the alveolar surfactant. The consequence of this wasted ventilation is arterial hypoxemia. The obstruction of the pulmonary circulation also results in the reduction in cross-sectional area of the pulmonary arterial bed available for the flow of blood from the right ventricle. This loss of vascular capacity leads to elevation of pulmonary arterial pressure and a hemodynamic burden in the form of pressure overloading of the right ventricle. Usually the elevation of pulmonary arterial pressure is mild to moderate and not severe as the right ventricle is not able to generate a greater systolic pressure under the acute hemodynamic burden. The pulmonary circulation may be compromised to a greater extent than might be expected on the anatomic basis (size of the thromboembolus) due to humoral influences (release of serotonin from platelets in the emboli) and other reflex influences.

The effect of the pulmonary embolism on the cardiopulmonary status of the patient is determined not only by the severity of the embolism but also by the presence or absence of underlying cardiac or pulmonary disease. The lung normally obtains oxygen from three sources: the pulmonary arterial circulation, the bronchial arterial circulation and the alveoli. Pulmonary infarction occurs predominantly in subjects with underlying cardiac or pulmonary disease who have large pulmonary emboli. The vast majority of pulmonary emboli resolve by natural fibrinolysis or by the process of organisation over a period of 10–14 days.

Clinical features Pulmonary embolism may present as one of four clinical syndromes. *Massive* pulmonary thromboembolism is defined as sufficient obstruction of the pulmonary arterial blood flow causing substantial increase in right ventricular afterload. It is usually due to a large proximal pulmonary embolus in the main or branch pulmonary arteries. The features of this syndrome include syncope, profound dyspnea of acute onset, cardiogenic shock or even cardiac arrest. The patients frequently display tachycardia, tachypnea, hypotension and are cyanosed. Pleuritic chest pain is not a feature of massive pulmonary thromboembolism. *Submassive* pulmonary thrombembolism is defined as embolism of one or more pulmonary vascular segments not accompained by elevation in the right ventricular pressures. The most frequent symptom is pleuritic chest pain. When there is embolism which is unilateral and to a distal branch of the pulmonary arterial

circulation, pulmonary infarction may occur. Intense pleuritic chest pain which tends to be unilateral is an important clinical feature and typically develops 3–7 days after the onset of embolism. The fourth syndrome of presentation may be as chronic pulmonary arterial hypertension due to recurrent pulmonary thromboemboli which have not been identified clinically. Other occult presentations where a diagnosis of pulmonary embolism should be considered include sudden worsening of preexisting congestive heart failure, or repetitive bouts of unexplained supraventricular tachyarrhythmias.

The physical examination may be deceptively normal in a patient with pulmonary embolism. Tachycardia is the single most consistent finding. Signs such as a loud pulmonary closure sound or a prominent right ventricular gallop are uncommon. The detection of coexistent deep venous thrombosis is an excellent clue to the possibility of pulmonary embolism but its absence does not exclude the diagnosis of pulmonary thromboembolism. Fever is uncommon unless there is associated pulmonary infarction or infection.

Investigations Routine laboratory tests are rarely helpful in the diagnosis of pulmonary embolism. In the absence of pulmonary infarction, leucocytosis or elevation of erythrocyte sedimentation rate are rarely present. Among the newer tests which have become available and which appear promising is the measurement of *d-dimer* levels in the blood. Endogenous fibrinolysis of cross-linked fibrin in pulmonary embolism leads to the release of unique products into the bloodstream identified as the *d-dimer fragment*. However, elevation of d-dimer may be present in deep venous thrombosis of the legs as well. Currently this test is not routinely available in India.

The ECG is very often normal in patients with pulmonary thromboemboli (other than for tachycardia). Occasionally, there may be evidence of right axis deviation, tall P waves and the $S_1Q_3T_3$ pattern (S in lead I, Q in lead III with inverted T waves). The chest X-ray may show a parenchymal infiltrate and evidence of a pleural effusion if pulmonary infarction has occurred. There may be diminished volume of a lower lobe of the lung resulting in displacement of a major fissure or an elevation of the hemidiaphragm. A difference in diameter of the hilar vessels on the two sides should raise the suspicion of pulmonary embolism. Occasionally there may be abrupt cut-off of a vessel and distal radiolucency in the lung zones. It needs to be emphasised that a normal chest X-ray is the most common finding in pulmonary thromboembolism and in no way excludes the diagnosis. The analysis of arterial blood gases shows evidence of arterial hypoxemia, hypocapnia and respiratory alkalosis. Arterial hypoxemia is thus a useful clue though it is non-specific and may be absent in a small percentage of patients even in the presence of significant pulmonary embolism.

Ventilation-perfusion lung scanning (see section 12.3) is one of the key diagnostic tests in screening for pulmonary thromboembolism. A normal perfusion scan essentially rules out pulmonary embolism. If there are defects on the perfusion scan which are segmental or larger in size, a ventilation scan should be performed to check whether the size of the defect on the perfusion scan matches the size of the defect on the ventilation scan. In pulmonary thromboembolism there is usually a mismatch with a normal ventilation scan and large segmental perfusion defects on the perfusion scan. If the defects on the perfusion scan are subsegmental in size, the ventilation scan will not be useful as this perfusion scan is non-diagnostic and pulmonary angiography is required. If there is a strong clinical suspicion of pulmonary embolism and the ventilation perfusion scan is non-diagnostic, B-mode ultrasonography of the leg veins may be used for the detection of deep venous thrombosis in the legs. If in this situation the sonogram is abnormal then it is very probable that the

clinician is dealing with a clinical situation of pulmonary thromboembolism. However, if the clinical suspicion is high and both the ventilation-perfusion scan and the sonogram of the leg veins are non-diagnostic, then the only definitive means of diagnosing pulmonary thromboembolism is pulmonary angiography. The most common finding on the pulmonary angiogram are filling defects in the pulmonary arteries. The other diagnostic sign which is less often seen is the abrupt cut-off of a pulmonary vessel at the point of embolic infarction. Two-dimensional echocardiography and Doppler echocardiography may sometimes be useful in the diagnosis of pulmonary embolism. Evidence of a dilated hypokinetic right ventricle, a flattened interventricular septum, a small, under-filled left ventricle and the presence of tricuspid regurgitation with an increased flow velocity compatible with mild to moderate pulmonary arterial hypertension are the key diagnostic features on the echocardiogram.

Treatment Initially, administration of heparin is the treatment of choice for pulmonary thromboembolism. The goals of therapy include inhibition of growth of the thromboemboli with promotion of resolution and the prevention of recurrence. Heparin may be administered either as a continuous intravenous infusion of 1000 units per hour or may be given as an intermittent bolus of 5000 units every four hours. An effective alternative is the use of subcutaneous heparin at the dose of 5000 units every four hours. An attempt is made to keep the clotting time or the partial thromboplastin time (PTT) at 1.5–2 times the control value during the administration of heparin. On the second or third day of heparin therapy, oral anticoagulants can be begun aiming for a prothrombin time of between 1.5–1.8 times the control (Fig 12.72). The role of thrombolytic agents (streptokinase, urokinase, tissue plasminogen activator) in the management of acute pulmonary embolism is still not well-defined. Thrombolytic agents may have an advantage in patients with massive pulmonary embolism and cardiogenic shock in whom surgical embolectomy would otherwise be an effective alternative. When pulmonary

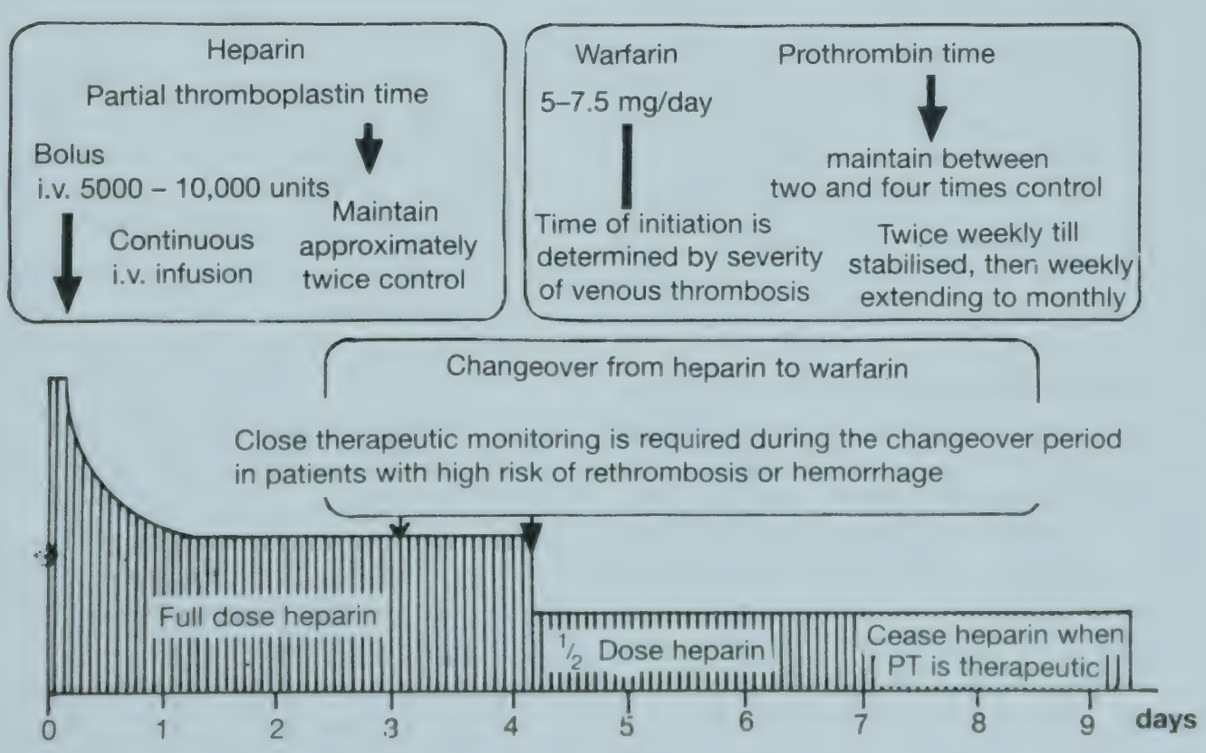


Fig 12.72 Treatment for thromboembolism

thromboembolism is recurrent due to recurrent lower extremity venous thromboembolism, insertion of a filter into the inferior vena cava may be considered an effective therapeutic alternative.

Prognosis The prognosis for a patient with pulmonary embolism who is treated with heparin is excellent. Untreated pulmonary embolism can result in death in 10–25 per cent of patients.

Prevention Because pulmonary embolism is difficult to diagnose, expensive to treat and occasionally lethal, the most effective method for treatment of pulmonary thromboembolism is prevention of the disease. Prophylactic use of small doses of subcutaneous heparin in the clinical high risk categories mentioned earlier is one of the methods of preventing pulmonary thromboembolism. Pharmacological measures of prophylaxis may be combined with mechanical measures like the use of graded compression stocking in patients who are undergoing surgery. The use of heparin for prophylaxis has resulted in a reduction of pulmonary thromboembolism by 40–60 per cent in controlled clinical trials.

KEY CONCEPTS

Pulmonary hypertension

- Pulmonary arterial hypertension is defined as mean pulmonary arterial pressure >25 mmHg. It may be postcapillary (left ventricular failure, MS, myxoma, veno-occlusive disease) or precapillary (primary pulmonary hypertension, cor pulmonale, cardiac shunt lesions, Eisenmenger syndrome).
- The symptoms include exertional dyspnea, right-sided chest pain (angina-like), syncope, hemoptysis and RUQ abdominal pain (hepatic congestion). Raynaud's phenomenon may be a feature of primary pulmonary hypertension and of immunoinflammatory diseases.
- The physical findings include a parasternal lift, a loud P_2, right-sided S_3, murmur of TR, jugular venous distension (prominent a waves) with a palpable pulsatile liver.
- The ECG shows P pulmonale and RVH. The chest X-ray shows a large main pulmonary artery segment; pulmonary venous hypertension may be evident if there is postcapillary pulmonary hypertension. The echocardiogram is helpful in excluding associated mitral valve disease, quantitating the PA pressure (from the TR jet velocity) and for excluding shunt lesions (contrast studies). A ventilation-perfusion scan may be useful for documenting multiple pulmonary emboli.
- The treatment depends on the etiology of pulmonary hypertension. These measures may include oxygen supplementation for cor pulmonale, definitive relief of left-sided disease (such as MS) and vasodilators (prostacyclins, etc.) in primary pulmonary hypertension. Oral anticoagulants are recommended in patients with primary and thromoboembolic pulmonary hypertension. Heart-lung transplantation may be considered for end stage lung disease or in select patients with primary pulmonary hypertension.

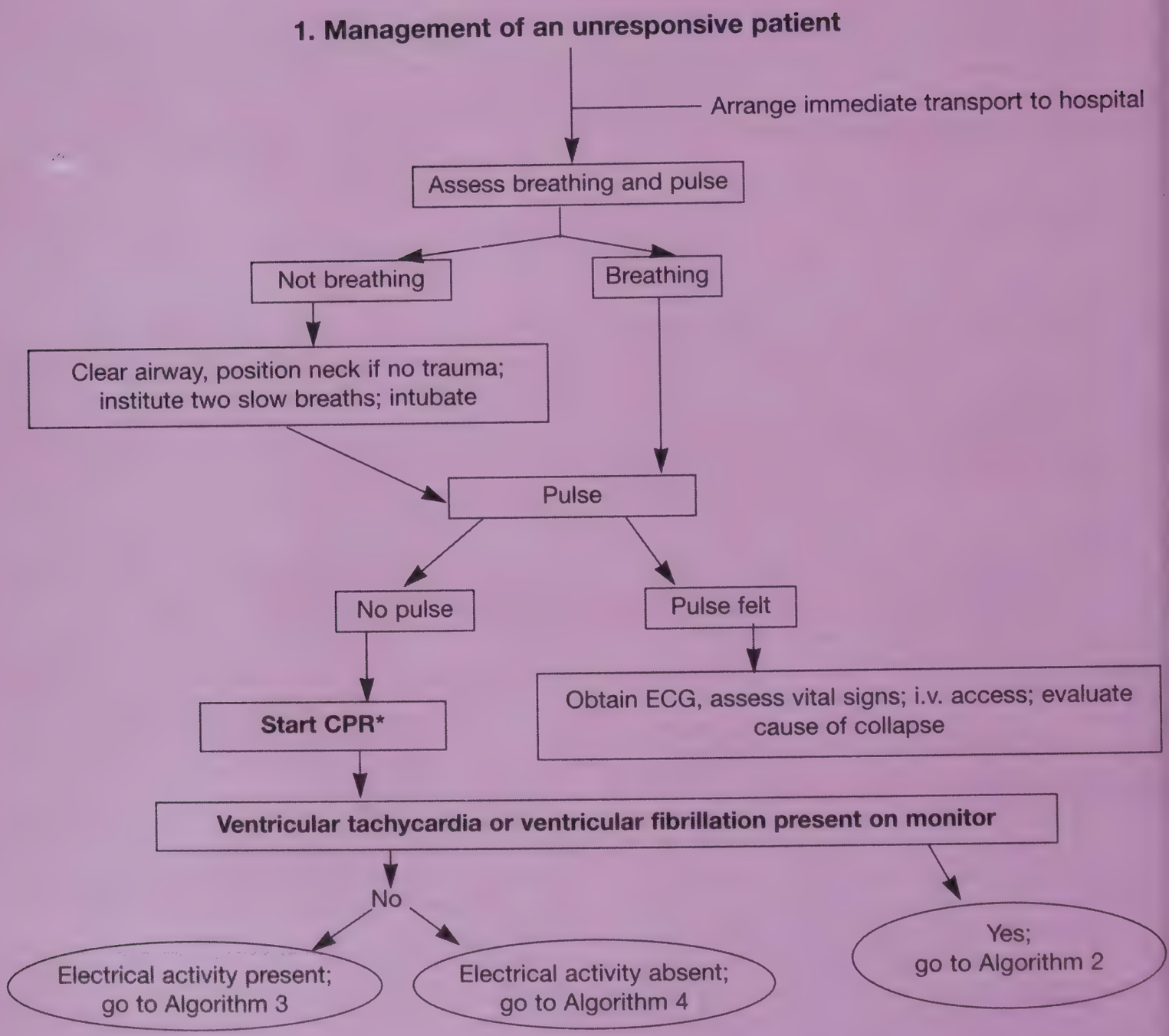
Cor pulmonale

- Cor pulmonale refers to RV hypertrophy/disease resulting from pulmonary hypertension secondary to pulmonary disease. Cor pulmonale may be acute (as in pulmonary embolism) or chronic (COPD, interstitial fibrosis, sleep apnea, hypoventilation).
- The possible mechanisms of pulmonary hypertension include hypoxia, acidosis (e.g., COPD; correlates include FEV_1 <1 litre, P_aO_2 <55 mmHg) and vascular obliteration (as in recurrent embolism).
- The symptoms are those of right-sided heart failure and the physical findings are those of pulmonary hypertension.
- The chest X-ray reveals an enlarged pulmonary arterial segment with peripheral pruning. The ECG features include P pulmonale, right axis deviation, and right ventricular hypertrophy.
- The treatment includes supplemental oxygen delivery at night (for patients with COPD), diuretics (if there is systemic venous congestion) and phlebotomy (if the hematocrit is >55%).

Pulmonary thromboembolism (PTE)

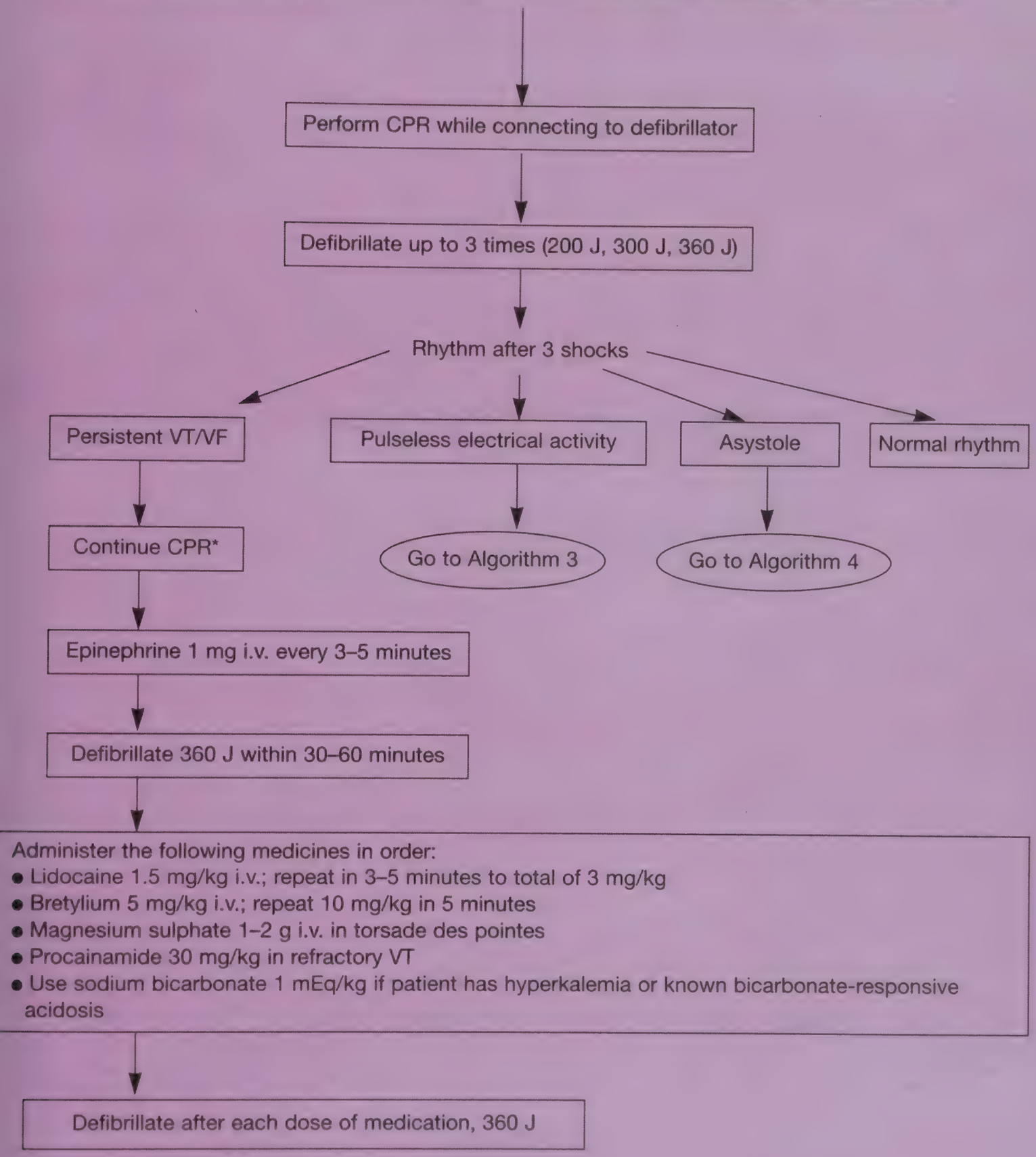
- About 90% of all pulmonary emboli arise from the leg veins. Prolonged bedrest, recent surgery, fractures, hypercoagulable states and oral contraceptive use have all been associated with PTE.
- The symptoms are notoriously non-specific. Dyspnea, tachypnea and hemoptysis occur with pulmonary infarction. Often there may only be mild fever and tachycardia. Massive PTE is associated with acute right heart failure, syncope or cardiovascular collapse.
- ABG reveals hypoxemia with respiratory alkalosis. An ECG is obtained to exclude MI; it usually shows tachycardia and non-specific ST-T changes; an $S_1Q_3T_3$ pattern is suggestive of PTE but is uncommon. The echocardiogram may show signs of acute right heart pressure overload.
- V/Q scan is the investigation of choice and is interpreted in conjunction with a chest X-ray ; results are reported as indicating a low, moderate or high probability of PTE. If the V/Q scan is equivocal, impedance plethysmography or Duplex ultrasound should be ordered (if available) to substantiate thrombi in the leg veins.
- Massive PTE with collapse is an indication for thrombolysis. Other cases are best managed with i.v. heparin, with a switch to oral anticoagulants continued for 3–6 months (or INR 2–4). IVC filters may be considered if PTE is recurrent, or if there is an absolute contraindication to the use of anticoagulants.
- Prevention is the best approach to DVT and PTE; subcutaneous heparin, elastic stockings, pneumatic compression, and minidose warfarin are some approaches.

12.14 Cardiovascular emergencies



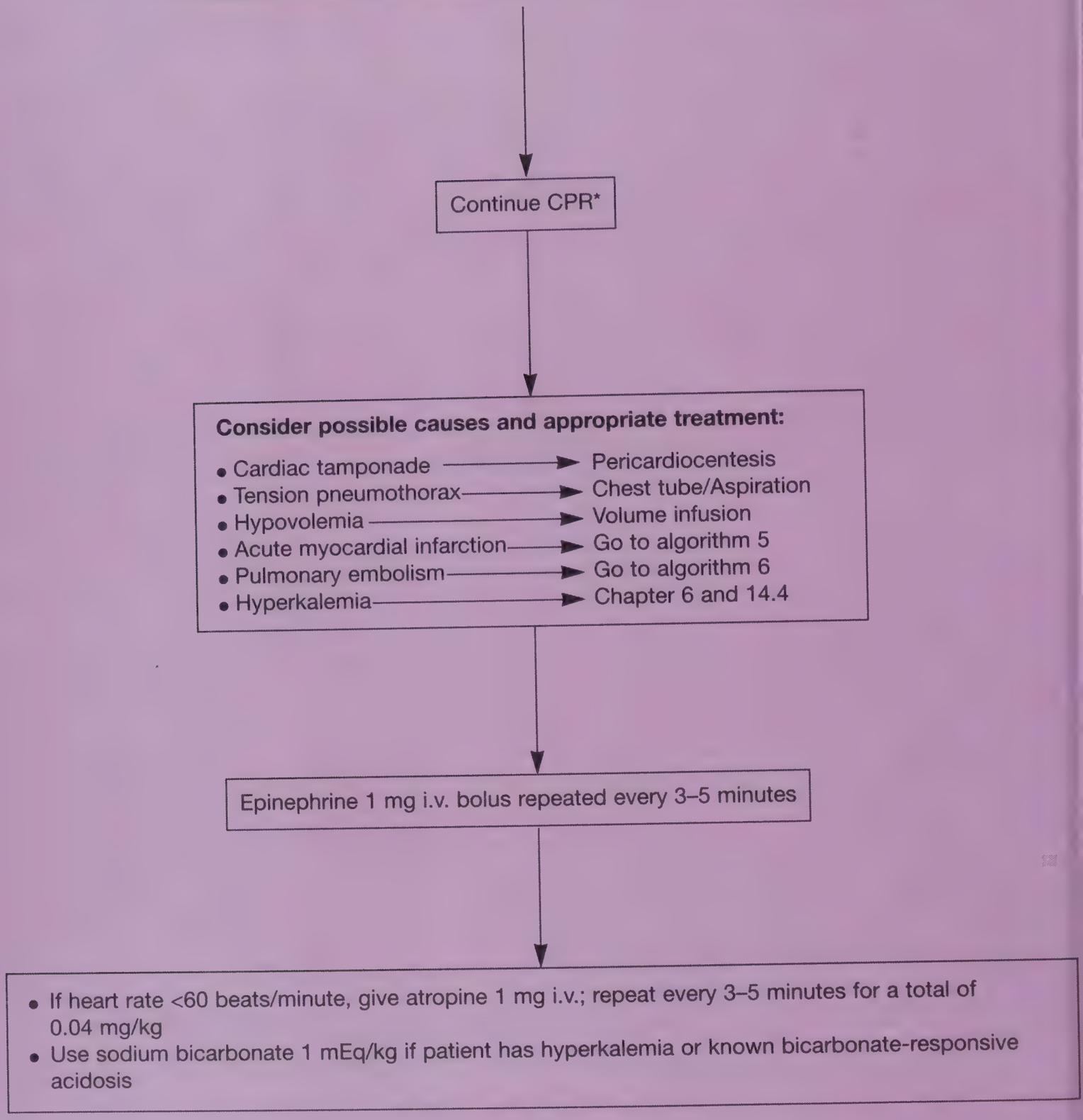
* CPR = Cardiopulmonary resuscitation (10 sequences of 5:1 ventilation/chest compression between therapeutic maneuvers)

2. Management of ventricular fibrillation or persistent ventricular tachycardia



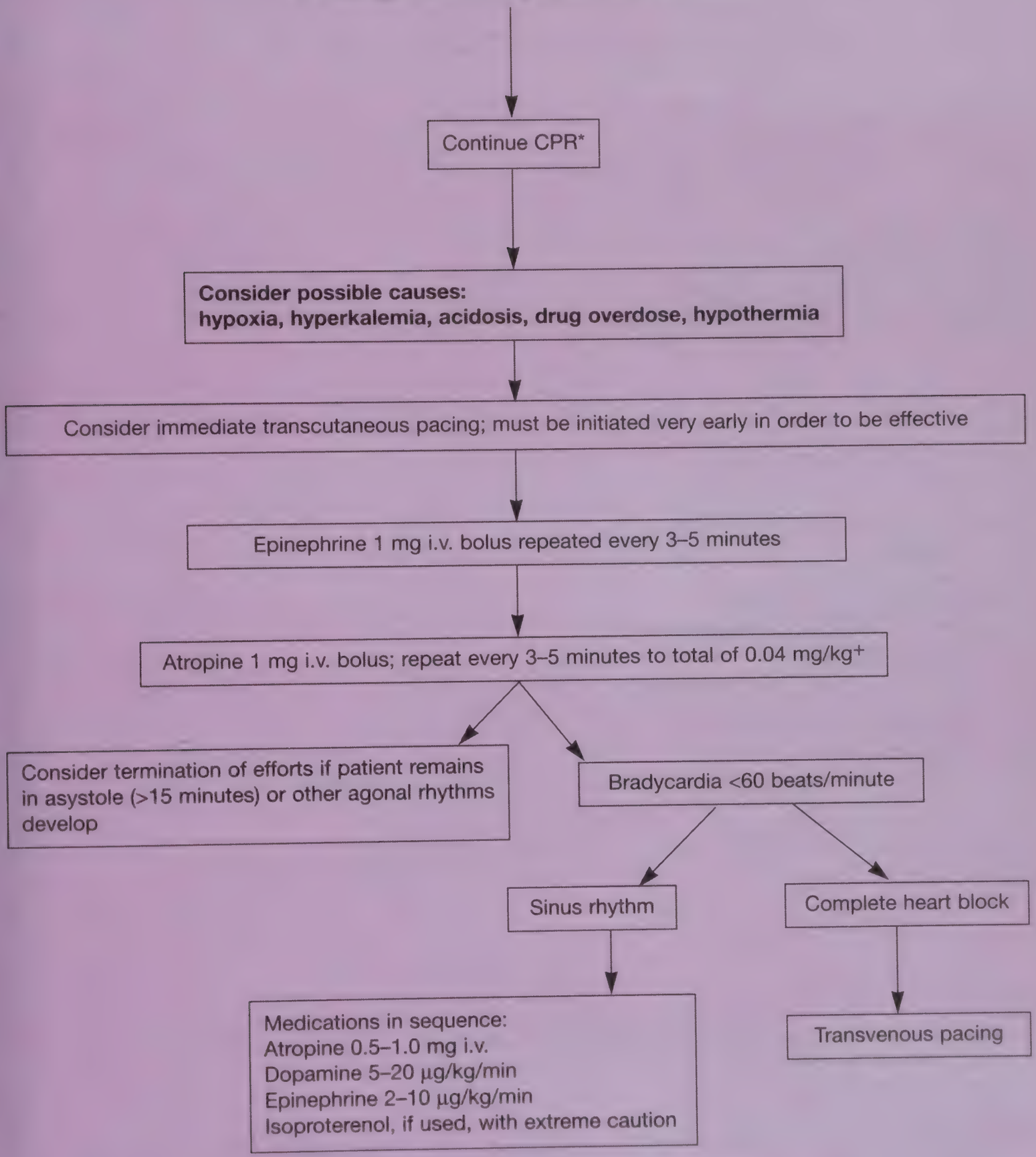
* CPR = Cardiopulmonary resuscitation (10 sequences of 5:1 ventilation/chest compression between therapeutic maneuvers).

3. Management of a patient with pulseless electrical activity



* CPR = Cardiopulmonary resuscitation (10 sequences of 5:1 ventilation/chest compression between therapeuti maneuvers)

4. Management of a patient with asystole



* CPR = Cardiopulmonary resuscitation (10 sequences of 5:1 ventilation/chest compression);
+ Some authorities recommend a single bolus of 3 mg.

5. Management of acute myocardial infarction

- Establish i.v. line;
- Monitor vital signs; blood for chemistry and enzymes
- Obtain 12-lead ECG; right-sided leads should be obtained

Decide on eligiblity for thrombolysis

Eligible:

acute Q-wave MI
< 6 hours of chest pain
no contraindication to streptokinase

Contraindications:

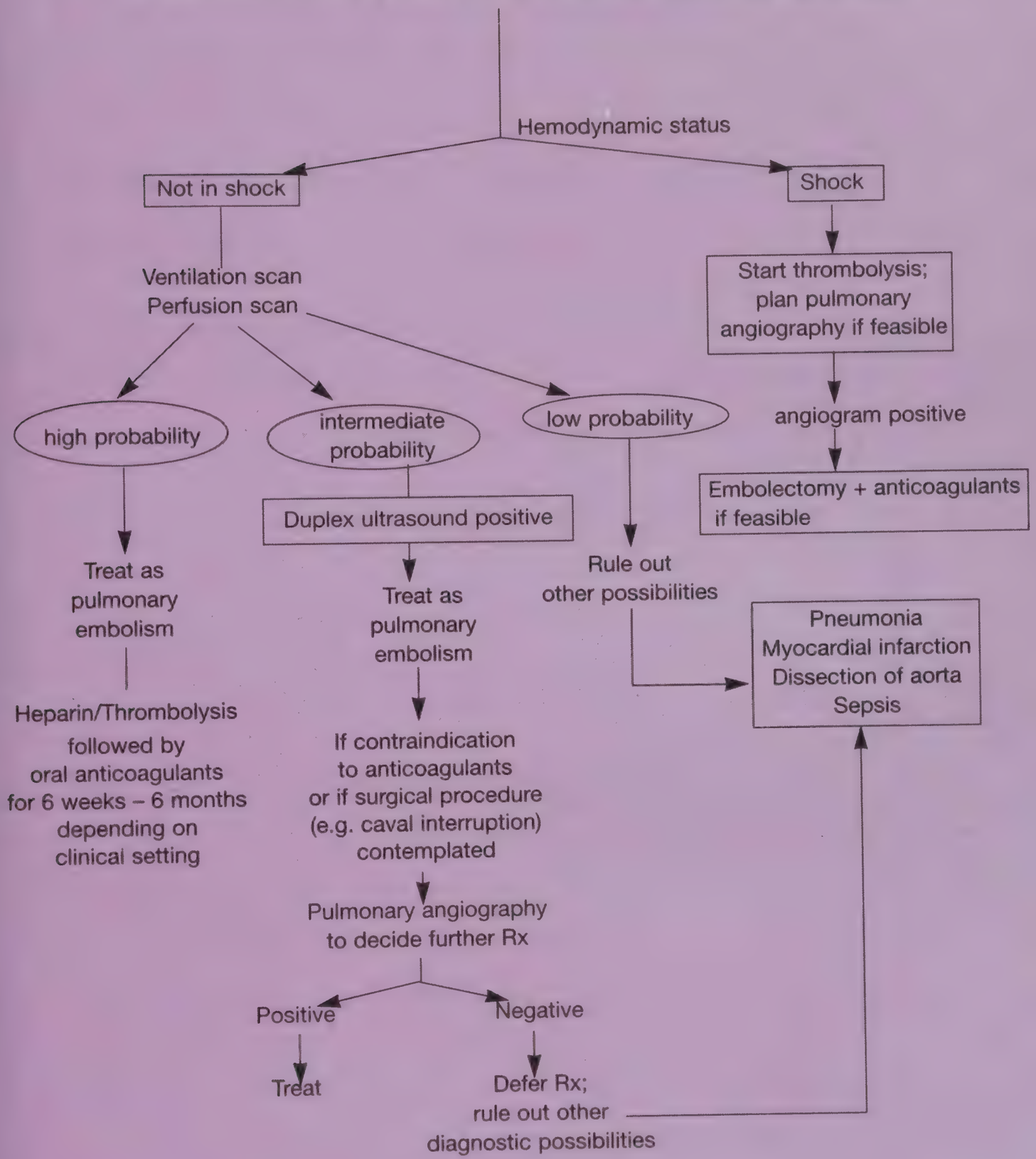
very recent trauma (major surgery, prolonged CPR)
recent stroke, GI bleed, or ulcer, BP>180/110 mmHg
known allergy to streptokinase

Precautions:

recent major surgery, obstetric delivery, puncture of non-compressible artery
chronic peptic ulcer
chest trauma, CPR

- **Oxygen inhalation; bedrest; stool softener; mild sedation**
- **Morphine i.v. for chest pain**
- **Chew aspirin tablet**
- **Nitrates for chest pain**
- **Nitroglycerin i.v. for ongoing ischemia**
- **Beta-blockers i.v.**
- **Consider ACE inhibitors if LVEF < 0.40**
- **Heparin especially if thrombolytic agent is tissue plasminogen activator**

6. Management of a patient with suspected pulmonary embolism



High probability : V/Q mismatch, lobar defect or multiple defects

Intermediate probability : V/Q mismatch, segmental defect

Low probability : V/Q match, subsegmental defect

7. Management of acute pulmonary edema

assess and treat precipitating causes

Emergency measures
- Prop up or sit on the edge of the bed
- Oxygen inhalation
- Morphine i.v. 3 mg repeat if necessary after 15 minutes, maximum of 15 mg
- Furosemide i.v. 0.5–1 mg/kg
- Nitroglycerin sublingual

Second line of action
- Nitroglycerin i.v. if BP > 100 mmHg; 10–20 µg/min;
  especially if active ischemia present; effective in non-ischemic too
- Nitroprusside i.v. if BP > 100 mmHg; 0.1–5 µg/kg/min;
  especially if due to valvular regurgitation or volume overload
- Dopamine if BP < 100 mmHg; 2.5–20 µg/kg/min
- Dobutamine if BP < 100 mmHg; 2–20 µg/kg/min

Additional measures
- Consider aminophylline 5 mg/kg if wheezing prominent
- Treat any arrhythmia
- Treat ischemia; thrombolysis if acute MI; angioplasty of culprit vessel if refractory unstable angina
- Consider intraaortic balloon pump for persistent hypotension (if available)
- Consider surgical revascularisation if all medical measures fail and ischemia is the etiology; valve replacement for acute valvular regurgitation related to endocarditis

13

Disorders of the Gastrointestinal and Hepatobiliary System

13.1 Basic gastrointestinal, hepatobiliary and pancreatic physiology

The Esophagus

The esophagus is a hollow tubular organ which begins as an upper esophageal sphincter after the oropharynx and extends into a body that varies from 18–25 cm in length. The esophageal body extends from the lower part of the upper esophageal sphincter upto the lower esophageal sphincter. The terminal part of the esophagus is the lower esophageal sphincter. The upper esophageal sphincter is an intraluminal high pressure zone composed of the cricopharyngeus muscle and the lowermost portion of the inferior pharyngeal constrictor muscle. There is, however, no histologic proof of a lower esophageal sphincter, which is basically an intraluminal high pressure zone.

The wall of the esophagus, like most other regions of the gastrointestinal tract, consists of an inner mucosa, muscularis mucosa, submucosa and muscularis propria. The mucosa is mainly stratified squamous epithelium. Occasionally in the distal esophagus the squamous epithelium is replaced by columnar epithelium—*Barrett's esophagus*. This has clinical importance mainly due to a thirty- to fortyfold increase in the risk of developing an esophageal carcinoma.

The innervation of the esophagus is by a vagal extrinsic plexus at the level of the mid-esophageal body, and an intrinsic plexus. The latter consists of a submucous plexus (of Meissner) that controls mucous secretion and a myenteric plexus (of Auerbach) located between the circular and longitudinal muscles of the muscularis propria. The myenteric plexus plays a key role in esophageal peristalsis.

The esophageal sphincter and body provide a mechanism for propelling a food bolus during swallowing and preventing retrograde flow of food between swallows. The acute angle of entry of the esophagus into the stomach and the compression of the intraabdominal esophagus by increased intraabdominal pressure are additional mechanisms that contribute to the prevention of the reflux of gastric acid into the esophagus (gastroesophageal reflux).

Gastric Anatomy and Physiology

The stomach consists anatomically of five parts: the cardia, the fundus, the body, the antrum and the pylorus. Histologically, it is composed of four tissue layers: the mucosa, the submucosa, the muscularis propria and the serosa. Its arterial supply is from the branches of the celiac axes: the left and right gastric arteries, the left and right gastroepiploic arteries and the short gastric arteries. The innervation is by the sympathetic and parasympathetic (vagal) nervous systems. Microscopically, the stomach contains at least

four different types of cells. The *parietal* or *oxyntic* cells located in the fundus and the body of the stomach secrete hydrochloric acid and the glycoprotein intrinsic factor. Pepsinogen is secreted by *'chief' cells* located in the fundus and the body, and by mucous cells located in the cardia, fundus, body and antrum. Agents such as histamine, gastrin and the vagal tone increase both acid and pepsinogen secretion. Secretin, however, augments pepsinogen secretion but inhibits acid secretion. The *'mucous cells'* are located in all regions of the stomach and secrete gastric mucous which is a thin viscoelastic gel consisting of glycoproteins, immunoglobulin A and blood group substances (A, B, H). It traps bicarbonate and retards the back diffusion of hydrogen ion from the luminal surface. The *'G' cells* secrete gastrin into the luminal contents of the stomach and are mainly located in the gastric antrum.

The main functions of the stomach include grinding and mixing food with gastric secretions, and the secretion of digestive juices and acid. Phasic myogenic contractions bring about mixing and food is converted into a homogenous *'chyme'*. Gastric emptying is regulated by neural and hormonal influences. Vagal tone, gastrin, cholecystokinin and motilin enhance motility, whereas glucagon, secretin, gastric inhibiting polypeptide (GIP) and vasoactive intestinal polypeptide (VIP) inhibit contractions in the distal stomach and retard gastric emptying.

Hydrochloric acid is secreted by the parietal or oxyntic cells and serves to convert pepsinogen into the active form pepsin which facilitates protein digestion. Gastric acid secretion has three phases: the *cephalic* phase is evoked by the sight and smell of food, is mediated through the vagus nerve and accounts for 30 per cent of total acid secretion. The *gastric phase* is mediated by gastric distension and the chemical composition of food. It contributes the bulk (>50%) of acid secreted. The *intestinal phase* is initiated by intestinal distension and the end products of protein digestion. The integrity of the gastric mucosa is maintained in a milieu of acidity by the protective effects of the mucous (which slows the back-diffusion of H^+ ions) and bicarbonate (which neutralises H^+ ions). Prostaglandins increase the production of mucous and bicarbonate, while alcohol and non-steroidal antiinflammatory drugs reduce their production. Mucosal resistance is also determined by the mucosal blood flow.

The Pancreas

Anatomy The pancreas lies transversely in the retroperitoneum. It has a head that rests in the curvature of the duodenum and a body that extends into a tail which touches the splenic hilum. It has dual blood supply from the celiac axis and the superior mesenteric artery. It is innervated by sympathetic nerves of the celiac ganglia and parasympathetic nerves passing from the vagus.

Histologically the pancreas consists of units of exocrine cells clustered about a ductule forming an *'acinus'*. The ductules merge to form larger ducts that further merge to form a major and a minor pancreatic duct. The exocrine cells secrete several digestive enzymes and the ductular epithelium secretes bicarbonate. The *islets of Langerhans* are cells distributed throughout the pancreas and are separated from the acini by reticular fibres. The islets contain a mixed population of three granular cell types—insulin secreting *beta* cells, glucagon secreting *alpha* cells and somatostatin secreting *delta* cells.

Physiology The pancreas secretes about 1500 ml of digestive juices in a day with an average content of sodium of 145 mEq/L, potassium of 5 mEq/L and chloride plus bicarbonate of 155 mEq/L. The pH of pancreatic fluid is alkaline (6.6–8.2). This neutralises the acid from the stomach and is the optimal pH for most pancreatic enzymes. Pancreatic enzymes are synthesised in the endoplasmic reticulum of the acinar cells, are stored in zymogen granules, and are released by exocytosis.

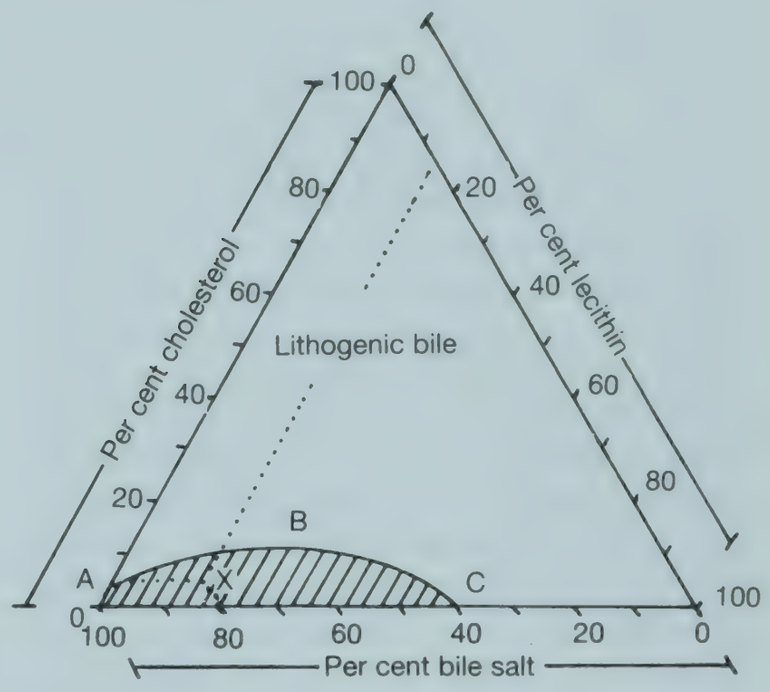


Fig 13.1 Three major components of bile (bile salts, lecithin, and cholesterol) displayed on triangular coordinates. Line ABC represents the maximum solubility of cholesterol in varying mixtures of bile salt and lecithin. Point X represents normal bile composition, containing 5% cholesterol, 15% lecithin, and 80% bile salt. Bile having a composition falling above the shaded zone would contain excess cholesterol in either supersaturated or precipitated form (crystals or liquid crystals).

Fig 13.1 Cholesterol, lecithin and bile salt in bile

Pancreatic enzymes include proteases (trypsin, chymotrypsin, carboxypeptidase, elastase), amylases, lipase and phospholipase. Pancreatic secretion is controlled by the hormones secretin and cholecystokinin, and by vagal parasympathetic neural influences. Secretin is a peptide hormone released by the *'S' cells* of the upper small intestinal mucosa under the stimulus of acidification of the duodenum. Secretin produces a pancreatic fluid which is rich in bicarbonate and low in enzymes, by primarily stimulating ductular epithelium, whereas cholecystokinin (also produced by proximal small intestinal mucosa) stimulates acinar cells resulting in an enzyme-rich secretion that is relatively low in bicarbonate content.

Deficiency of pancreatic lipase leads to incomplete hydrolysis of fat; this is the earliest and clinically the most relevant manifestation of exocrine pancreatic insufficiency. Steatorrhea, however, occurs only when 90 per cent of the pancreatic acinar tissue is destroyed.

The Gallbladder and Biliary Physiology

Bile is formed by the secretion of water and solutes across the canalicular membrane of the hepatocyte with a further alteration of composition due to secretion and reabsorption by bile ductular and gallbladder epithelial cells.

The two principal functions of bile are the excretion of cholesterol, and delivery of bile salts to the intestinal lumen to aid in fat digestion and absorption. Cholesterol is intrinsically poorly soluble in water. Its molecular association with amphiphilic[1] lipids in bile lecithins and bile salts enhances its solubility a millionfold. This solubilisation of cholesterol is either in the form of mixed lipid *'vesicles'* or in the form of mixed disc *'micelles'*. Mixed lipid vesicles are about 500 Å in diameter and composed primarily of lecithin and cholesterol with lesser amounts of bile salt. Mixed disc micelles measure 50 Å in diameter and are composed of more bile salts and lesser lecithin. The amounts of cholesterol, lecithin and bile salt in any sample of bile can be

[1] An amphiphilic molecule has functional groups that confer both lipid and water solubility.

plotted on triangular coordinates (Fig 13.1). Bile that has a composition falling outside the shaded area cannot solubilise additional cholesterol and is said to be *lithogenic.*

The bile salts synthesised by the hepatocytes include cholic acid and chenodeoxycholic acid. These are the *primary* bile salts and are conjugated with an amino acid, either glycine or taurine. The conjugated bile salts are stored in the gallbladder and released into the intestinal lumen when the gallbladder contracts. In the alkaline intestinal pH, bile salts are ionised and participate in fat absorption. Primary bile salts undergo dehydroxylation by bacterial flora to form *secondary* bile salts–deoxycholic and lithocholic acid–in the intestinal lumen. Bile salts are reabsorbed by a receptor mediated process in the terminal ilium to return to the liver via the portal vein. This cycle is called the *enterohepatic circulation* of bile salts. Bile salts are synthesised in the liver from cholesterol and the process is under control by the negative feedback inhibition of the returning bile salts from the gut.

Hepatic Anatomy and Physiology

The liver is the largest organ in the body weighing between 1200 and 1500 grams. Though anatomically the falciform ligament divides the liver anteriorly into a large right and a smaller left lobe, the true physiological right and left lobes are equal in size and the interlobar plane extends between the gallbladder fossa and the fossa of the inferior vena cava. Such a division is based on the primary branching pattern of hepatic arterial and venous systems. Each lobe has independent blood supply with essentially no collateral circulation between them.

The liver has a dual blood supply with about 30 per cent of hepatic blood flow provided by the celiac axis by way of the hepatic artery and the remainder being provided by the portal vein. Both sources terminate in the hepatic sinusoids. The drainage of venous effluent is through three major hepatic veins which drain into the inferior vena cava. The innervation of the liver is from the vagal nerves and the celiac plexus.

Microscopically, the *classical* hepatic lobule has been described as one where peripheral portal tracts surround a central vein and the hepatocytes are arranged as single-cell plates. The *acinar concept* of the hepatic lobule pictures the hepatic veins at the periphery of the acinus, with blood flow from the central hepatic artery and portal vein towards the peripheral venules. The central acinar zone has cells with abundant mitochondria and is rich in enzymes of the citric acid cycle. The peripheral acinar cells are more vulnerable to ischemia, and are richer in rough endoplasmic reticulum, because they are the sites of protein, triglyceride and lipoprotein formation.

The liver plays the central role in bilirubin metabolism, glucose homeostasis, synthesis of plasma proteins, lipids, lipoproteins and bile acids, storage of vitamins (A,D,E,K) as well as in the biotransformation and detoxification of numerous endogenous and exogenous compounds.

Bilirubin is a straight chain tetrapyrrole compound principally derived from the hemoglobin heme of senescent red cells. The iron and globin component of hemoglobin is removed and the resultant heme converted to biliverdin by the 'opening' of the porphyrin ring by the enzyme heme oxygenase. Biliverdin is converted to bilirubin by biliverdin reductase. The hepatic transport of bilirubin involves an initial binding to a cytoplasmic protein called *ligandin* followed by a two-stage conjugation to a diglucuronide derivative by the enzyme *glucuronyl transferase.* This is followed by excretion into the bile canaliculus. A defect in canalicular transport results in conjugated hyperbilirubinemia (*Dubin-Johnson syndrome*). A complete or partial absence of the enzyme glucuronyl transferase results in the *Crigler-Najjar syndrome.* In the *Gilbert syndrome* unconjugated hyperbilirubinemia occurs and is related to defective hepatic bilirubin uptake, partial deficiency of glucuronyl transferase, and

hemolysis (each factor contributing variedly in a given patient).

Small Intestine Anatomy and Physiology

The small intestine is approximately 6 m long. The first part is the duodenum which extends from the pylorus upto the ligament of Treitz. The mucosa of the duodenum differs from that of the rest of the intestine due to the presence of *Brunner's glands*. The boundary between the jejunum and the ileum is not discrete; by convention the proximal two-fifths is designated as the jejunum. The jejunum is smaller in calibre and its mucosa has more prominent *'valvulae conniventes'* in comparison with the ileum. The arterial blood supply is from the branches of the superior mesenteric artery and the venous drainage is into the portal venous system. The lymphatic drainage is through the thoracic duct.

Carbohydrate digestion and absorption

Polysaccharides such as starch, disaccharides (lactose and sucrose) and monosaccharides (glucose, fructose) constitute the dietary carbohydrates. Amylose and amylopectin, the principal components of starch, are digested by salivary and pancreatic amylases into *limit dextrins*[1] and di/trisaccharides. The absorptive microvillus membrane contains the enzymes limit dextrinase and disaccharidase which generate monosaccharides. Certain monosaccharides–glucose, galactose, fructose–are actively transported across the brush border by transporters that require energy provided by the Na^+–K^+ ATPase pump at the basolateral surface of the cells. Malabsorption of carbohydrates is therefore a result of damage to the microvillus' absorptive surface or due to congenital deficiency of disaccharidases or the transporters.

Protein digestion and absorption

Hydrolysis of dietary protein begins in the stomach with the action of gastric pepsin. The resultant polypeptides and amino acids release cholecystokinin, the major stimulus for the release of pancreatic proteases. The microvillus enzyme enterokinase is released by bile salts and converts trypsinogen to trypsin. Trypsin autocatalytically activates the other endopeptidases[2] (trypsin, chymotrypsin, elastase) and exopeptidases[3] (carboxypeptidase). The end products of protein digestion are amino acids and oligopeptides. The transport mechanisms for amino acids require energy and are stereospecific for L-isomers of the amino acids. There is evidence for a separate carrier mechanism for neutral, basic and dicarboxylic amino acids. Defects in these carrier mechanisms can result in malabsorption of the specific amino acids, for example, malabsorption of neutral amino acids in *Hartnup's disease.*

Fat digestion and absorption

Most dietary fat consists of long chain triglycerides. Although fat digestion begins in the stomach under the effect of lingual lipase, the principal site of digestion is the proximal small intestine under the influence of pancreatic lipase, bile salts and in an alkaline environment. Pancreatic lipase, facilitated by colipase, attaches to the surface of triglyceride droplets and hydrolyses them into free fatty acids, 2-monoglycerides and glycerol. Bile salt micelles incorporate the products of digestion to yield *'mixed micelles'* which cross the microvillus membrane. In the cytoplasm of the mucosal cells, fatty acids are activated to acyl CoA in the smooth endoplasmic reticulum. Fatty acyl CoA is esterified with a glycerophosphate to triglyceride and phospholipid. Chylomicrons are assembled largely in the Golgi region from the triglycerides, phospholipids, cholesterol esters and apoproteins. Chylomicrons enter the mucosal lymphatic channels (the lacteals) and then get distributed. Medium chain triglycerides

[1] Limit dextrins consist of 4–10 glucose molecules.

[2] Endopeptidase hydrolyses peptide bonds in the interior of proteins.

[3] Exopeptidase hydrolyses peptide bonds at the termini of proteins.

(6–10 carbon containing fatty acids) are, however, absorbed intact by the mucosa. They are, therefore, ideal dietary supplements in patients with fat malabsorption due to mucosal disease.

Intestinal water absorption

Of the nine litres of secreted digestive juices, 7–8 litres are reabsorbed in the small intestine, with colonic absorption of about 1–2 litres.

Absorption of other nutrients

Iron and calcium are both absorbed in the duodenum and proximal jejunum. Vitamin B_{12} (cobalamin) is absorbed in the distal ileum and the process requires the presence of the intrinsic factor, a glycoprotein secreted by gastric parietal cells.

Anatomy of the colon

The large intestine measures about 1.5 m in length. Its proximal part is the cecum which has a wide lumen. The luminal diameter progressively narrows from the ascending, transverse, descending colon to the sigmoid colon. The terminal part, the rectum, also has a wide lumen.

The arterial supply of the colon is through the superior and inferior mesenteric arteries and the venous effluent is through the superior and inferior mesenteric veins (portal circulation). The rectum is, however, partly drained by means of the systemic circulation by way of the hemorrhoidal veins.

The two areas of the colon that are more susceptible to ischemia are the splenic flexure (junction of the supply from the superior and inferior mesenteric arteries) and the rectosigmoid (junction of the supply from the inferior mesenteric and internal iliac arteries). The mucosal surface of the colon is smooth in contrast to the small intestine and consists of simple tubular glands. The longitudinal muscle of the colon is collected into three distinct bundles called *taenia coli*. The taenia cause puckering of the wall (*haustra*).

The nerve supply of the colon is from the autonomic nervous system. The parasympathetic supply is from the vagus, sacral nerves and the nervi erigentes. The sympathetic supply is by way of the splanchnic nerves and the hypogastric plexus.

The principal functions of the colon are water reabsorption (proximal part), storage of the feces (distal part) and defecation (terminal part). Most of the water is absorbed by the cecum and the ascending colon. About 1000 ml of water, 200 mEq of sodium and 150 mEq of chloride are absorbed and about 5 mEq of potassium are secreted by the colon; only 100 ml of water finally reaches the rectum. The semisolid feces is thereby converted to its solid form. The colon also contributes to absorption of bile acids (5–10% of enteric reabsorption). Considerable bacterial activity occurs in the colon. The colonic bacteria ferment and putrefy the fecal contents leading to the production of gases like carbon dioxide, methane, hydrogen, nitrogen and hydrogen sulfide. Amino acids are decarboxylated to produce toxic amines (*ptomaines*). Trytophan is converted into indole methylindole (skatole), the compound responsible for the characteristic odour of feces. The colonic microbial flora are also involved in the synthesis of ammonia, and vitamins K and B_{12}.

Gastrointestinal gas and motility

Bacterial fermentation results in the production of about 400 ml of gas in the intestines and is normally passed entirely rectally. Additionally some people under anxiety swallow a lot of gas which remains in the stomach and is expelled as a 'belch'. Many people complain of 'excess gas' and 'bloating'. These symptoms are erroneously attributed to 'gas' in the bowels. Usually these symptoms are related to abnormal intestinal motility. Localised areas of intestinal motor dysfunction, such as in the irritable bowel syndrome, result in spasm with resistance to transit of gas. This manifests as a feeling of bloating. On occasion, excess passage

of flatus is attributable to the consumption of large amounts of dietary fibre. Fruits, vegetables, and cereals eaten with their outer shells are a rich source of non-absorbable cellulose, hemicellulose, pectins and lignins; these undergo bacterial decomposition and gas production.

Gastrointestinal motility is determined in part by intrinsic 'electrical' myogenic pacemakers. The basic electrical rhythm in the gut originates in several pacemakers located in the proximal stomach (3 per minute), proximal duodenum (12 per minute) and the transverse colon (6 per minute). Whereas in the stomach and the small intestine the rate of the pacemaker generated potentials slows caudally, in the colon the rhythm spreads distally and proximally. These rhythms are influenced by food, dietary fibre content, gut hormones, and by neural (vagal and sympathetic) influences.

Gut hormones

More than thirty different hormones are produced by specialised cells within the gastrointestinal system. These cells have a special neuroendocrine function and are scattered throughout the gut. Their products are peptides which have a hormonal, paracrine or a neuromodulatory role. These peptides serve to integrate the secretory and motor functions of parts of the gut and also coordinate the roles of different parts of the gastrointestinal system so that it can function in an organised fashion. Table 13.1 represents some of these peptides and their roles.

Table 13.1 Gut peptides

Peptide (number of amino acids)	*Organ/cell of origin*	*Physiological role*
Peptides with a relatively clear role		
Gastrin (17,34)	G cells in the gastric antrum and intestine	increase gastric secretion, delay gastric emptying; increase lower esophageal sphincter tone
Secretin (27)	S cells of the duodenum	increase pancreatic bicarbonate secretion; decrease gastric emptying
Cholecystokinin (33,39,58)	I cells of the duodenum	increase pancreatic enzyme content of secretions; gallbladder contraction, relax the sphincter of Oddi; ? role in satiety
Glucose-dependent insulinotropic peptide (GIP, 42)	K cells of upper small intestine	increase insulin secretion; decrease gastric secretion
Motilin (22)	M cells of upper small intestine	increase gastric emptying, increase gut contraction
Somatostatin (14)	D cells of pancreas and gut	decrease intestinal secretion and hormone release
Vasoactive intestinal polypeptide (VIP, 28)	pancreas and gut (postganglionic nerves)	increase intestinal secretions and hormones; decrease small bowel and gastric emptying
Enteroglucagon (69) and colon	L cells of terminal ileum	inhibit gastric secretions and delay gastric emptying
Pancreatic polypeptide (36)	pancreas	decrease pancreatic and biliary secretion
Neurotensin (13)	N cells of terminal ileum and colon	inhibit gastric secretion, delay gastric emptying; increase pancreatic secretion
Peptides with an unclear role		
Neuropeptide Y (36)	gut myenteric plexus	decrease intestinal secretion, reduce colonic motility
Substance P (tachykinin, 11)	duodenum (myenteric plexus)	inhibit absorption, increase contraction
Bombesin (Gastrin-related peptide, 14)	stomach (myenteric plexus)	increase gastrin secretion, gastric secretion; increase cholecystokinin, motilin
Calcitonin-G-related peptide (37)	gut (intrinsic neurons)	inhibit gastric acid and pancreatic secretions, relax gut smooth muscle

13.2 Approach to a patient with gastrointestinal and liver disease

APPROACH TO A PATIENT WITH DYSPHAGIA

Dysphagia is the sensation of difficulty in swallowing. It is usually perceived as food or fluid sticking in the throat. It may be due to pharyngeal causes (*transfer* dysphagia) or esophageal causes (*transport* dysphagia). The term 'pseudodysphagia' refers to obstructive lesions beyond the cardia.

Pathophysiology The normal process of swallowing is initiated with a bolus of food being pushed back by the tongue into the pharynx. The pharynx then contracts while the upper esophageal sphincter relaxes. Symptoms which occur within one or two seconds of swallowing indicate a problem at this level—transfer dysphagia. The pharyngeal bolus then traverses the upper skeletal muscle part of the esophagus and the lower smooth muscle part largely under the influence of gravity. Auerbach's plexus coordinates the peristalsis with the relaxation of the lower esophageal sphincter ahead of the bolus. Symptoms produced from lesions beyond the upper esophageal sphincter are termed transport dysphagia.

Investigations A meticulous clinical history will permit a distinction between transfer and transport dysphagia. The onset of symptoms immediately after swallowing and the presence of associated nasal regurgitation, dysphonia and dysarthria (indicating associated dysfunction of other musculature innervated by lower cranial nerves) identify transfer dysphagia. Other features which are less specific include the presence of reduced salivation (Sjogren syndrome), associated skeletal muscle weakness (myopathy), gurgling with swallowing (pharyngeal pouch) or foul breath (tumour).

The causes of transport dysphagia are listed in Table 13.2. Since the innervation of the esophagus follows a dermatomal pattern, roughly half of the patients will accurately localise the level of obstruction. *Motor* dysphagia is typically intermittent, of long duration, affects fluids and solids equally, and is very often associated with some loss of weight. *Mechanical* dysphagia is continuous and dysphagia for solids precedes that for liquids; the presence of marked weight loss, duration of symptoms of less than one year and a rapidly progressive course identify a malignant etiology of mechanical dysphagia. The age of the patient is of some help too. Schatzki's ring (lower esophageal mucosal ring) is found in younger subjects, achalasia or esophageal spasm in the second to fourth decades, and carcinoma of the esophagus in the fifth decade and beyond.

Despite these distinctions, overlap in clinical manifestations is common. Symptoms can be intermittent in mechanical causes of dysphagia too, for example, in the pseudodysphagia syndrome produced by lesions below the cardia, in a lower esophageal ring, and in peptic strictures. In peptic strictures, the intermittent symptoms are related to the size of the bolus,

Table 13.2 Causes of dysphagia

	Transfer dysphagia (Oropharyngeal)	*Transport dysphagia (Esophageal)*
Mechanical causes		
	Carcinoma	Stricture
	Web	Carcinoma esophagus
	Fibrosis	Extrinsic tumour
	Abscess	Vascular
	Goitre	Schatzki ring (lower esophageal mucosal ring)
	Pharyngeal pouch	Benign tumour
	Foreign body	
Motor causes		
	Muscular dystrophy	Achalasia cardia
	Myopathies	Diffuse esophageal spasm
	Myasthenia gravis	Systemic sclerosis
	Lower cranial neuropathies	Muscular dystrophy
	Bulbar and pseudobulbar palsy	Autonomic neuropathy

a feature that should be sought carefully in the history; these are determined by the size of the bolus in relation to the luminal diameter of the structure and to the severity of associated spasm. A history of Raynaud's phenomenon, or associated esophageal reflux may suggest a cause of motor dysphagia such as progressive systemic sclerosis.

Although a physical examination is generally unrewarding, stigmata of systemic sclerosis or signs of neuromuscular disease may be evident. A local examination of the oropharynx and hypopharynx is essential for detecting structural abnormalities such as a web or a ring.

The key investigations are esophagogram, endoscopy and manometry. Often the esophagogram is the investigation chosen first as it provides information on the structure and the function of the esophagus. A diagnosis of transfer dysphagia is readily evident as are some causes of transport dysphagia such as an intraluminal web, a stricture, extrinsic compression or achalasia. Endoscopy is useful for taking biopsies from a suspicious structure and occasionally for therapeutic dilatation of a benign stricture.

Esophageal manometry is the investigation of choice for motor disorders of the esophagus, though the equipment is expensive and is available at only a few centres. *Achalasia* is identified by the presence of a 'hypertensive' lower esophageal sphincter that fails to relax by more than 30 per cent with swallowing, and an absence of peristalsis above the sphincter. *Diffuse esophageal spasm* is characterised by a lower esophageal sphincter pressure which is normal or elevated, a sphincter which relaxes fully with swallowing, and the striking appearance of numerous non-propulsive tertiary contractions.

Treatment Mechanical dysphagia is more amenable to treatment than motor dysphagia. Mechanical obstruction is relieved by surgical resection, bouginage, endoluminal prosthetic stenting or irradiation depending on whether the obstruction is due to a web, a stricture or a tumour, respectively.

Motor dysphagia has been treated with nitrates, anticholinergics, antacids and with sphincter ablation. Results have, however, been less than gratifying.

APPROACH TO A PATIENT WITH DIARRHEA

Diarrhea refers to frequent, loose stools. Quantitatively speaking, it refers to a daily stool weight exceeding 300 grams.

Pathophysiology Of the nine to ten litres of fluid entering the digestive tract daily (about two litres from ingested fluids and the rest from endogenous secretions) only 100–150 ml constitute a part of the stools (over 24 hours). About 50 per cent of this fluid entering the intestinal lumen is absorbed in the jejunum. Water absorption by the jejunal mucosa is not linked to sodium transport but is under the influence of postprandial osmotic gradients created by carbohydrate and aminoacid transport. Of the rest of the 4–5 litres, 75 per cent is absorbed by the ileal mucosa under the influence of a sodium pump. The remainder is absorbed in the ascending and transverse colon, being passively linked to active transport of sodium and chloride ions. Bicarbonate is secreted here in exchange for chloride ions.

Diarrhea may be due to an augmented intestinal secretion of water or due to a diminished reabsorption of water; it may also be due to an abnormally rapid transit of intestinal contents (Table 13.3). *Secretory diarrhea* refers to an increased intraluminal fluid content in the intestine due to excessive secretion. The secretory stimuli may be bacterial enterotoxins (cholera, *E.coli,* staphylococcal or clostridial infection) that increase cellular levels of cyclic adenosine monophosphate, gastrointestinal hormones (gastrin hypersecretion in Zollinger-Ellison syndrome, vasoactive intestinal polypeptide in pancreatic islet cell tumours), fatty acids, dihydroxy bile acids (diarrhea accompanying ileal resection) or anthraquinone cathartics. *Osmotic diarrhea* occurs in conditions associated with luminal hypertonicity (lactase deficiency[1]). Inflammatory bowel disease results in diarrhea by mucosal damage (which limits water reabsorption) and by actually increasing the volume of stools with blood, mucous and pus.

Both rapid and slow intestinal transit can result in diarrhea. Rapid transit time, seen in

[1] Undigested lactose cannot be absorbed. It remains in the lumen, the contents of which become hypertonic with respect to the extracellular fluid. Hence, body fluid is lost into the intestinal lumen.

Table 13.3 Causes of diarrhea

Large bowel diarrhea	*Small bowel diarrhea*
1. Inflammatory bowel disease	1. Malabsorption syndrome *
2. Infective colitis	2. Infective enteritis
E. histolytica	Giardia
Yersinia	Shigella
Campylobacter	Salmonella
3. Ischemic colitis	*E. coli*
4. Irritable bowel syndrome	3. Crohn's disease
5. Colorectal cancer	4. Intestinal tuberculosis
6. Multiple polyposis	5. Gastrinoma
7. Laxative abuse	6. Decreased intestinal transit time
8. Radiation colitis	Thyrotoxicosis
	Carcinoids

* See section on malabsorption for list of causes and classification.
Also see section 8.5 for clinical distinction of large and small bowel diarrhea

post-gastrectomy states and due to excess of certain hormones (thyroxine in hyperthyroidism, serotonin in the carcinoid syndrome), can result in diarrhea. Slow transit time as in patients with intestinal strictures, scleroderma, amyloidosis and intestinal pseudo-obstruction can also cause diarrhea. In these situations bacterial overgrowth is often present and results in diarrhea.

Diarrhea can also occur due to the outpouring of mucous, blood, serum proteins and pus from sites of mucosal inflammation and ulceration, for example, inflammatory bowel disease, infectious diarrhea produced by Shigella, Salmonella *Entameba histolytica.*

Treatment The key questions in the history are whether the diarrhea is acute or chronic, bloody or non-bloody, of small or large bowel origin, and functional or organic in nature. Diarrhea lasting for less than three weeks is considered *acute* and generally suggests an infective diarrhea. Diarrhea lasting for more than three weeks is *chronic* and may suggest inflammatory bowel disease, malabsorption syndrome or irritable bowel syndrome.

Whereas non-bloody diarrhea does not suggest a specific diagnosis, bloody diarrhea signifies mucosal damage either due to an enteroinvasive organism or due to non-infective inflammation of the bowel.

Certain clues in the history can help indicate whether the pathologic event is in the large or small bowel. Thus, small bowel diarrhea is of large volume or bulky, occurs less than six times per day; pain, if present, is often periumbilical. Large bowel diarrhea is small in amount, characteristically occurs more than six times per day, often accompanied by tenesmus (which signifies proctitis); pain, if present, is most often situated in the left lower quadrant of the abdomen.

The final question is whether a chronic non-bloody diarrhea is functional or organic. The presence of weight loss, nocturnal diarrhea, episodes of bloody diarrhea or incontinence characterise the diarrhea as being organic in nature.

The four common causes of chronic diarrhea in India are irritable bowel syndrome, intestinal parasitoses, abdominal tuberculosis and the malabsorption syndrome. A brief description of irritable bowel syndrome is provided here; the other conditions are discussed in detail later and in sections 13.5–13.6.

Irritable Bowel Syndrome

This is the commonest cause of chronic diarrhea in the outpatient department.

Clinical features Patients with this syndrome may present with diarrhea or constipation. They frequently experience abdominal distension and flatulence too. They may have abdominal pain which is relieved by defecation. They tend to have more frequent and more loose bowel movements with the onset of pain. Young adults are affected more often and there is a female predominance.

Pathophysiology The subset of patients with pain predominance show a greater frequency of high amplitude pressure contractions of the colon, and have chronic constipation whereas the *diarrhea-predominant* subset of patients show low amplitude contractions. Since myoelectric activity is abnormal, it has been suggested that the basic abnormality in irritable bowel syndrome may be in the smooth muscle. A heightened visceral perception and psychological stress are contributory factors.

Diagnosis and treatment The intermittent nature of symptoms without evidence of physical deterioration and the relation to stress suggest the diagnosis. Reassurance is an important component of management. Constipation responds to bulk cathartics and diarrhea to codeine phosphate (loperamide can be used in intractable diarrhea). Antispasmodics (mebeverine, peppermint oil) are indicated for disabling abdominal pain.

APPROACH TO A PATIENT WITH CONSTIPATION

Constipation is arbitrarily defined as the passage of less than three stools per week. Other definitions such as 'feeling of incomplete evacuation' or 'excessively hard stools' are difficult to evaluate objectively.

Pathophysiology Constipation can be associated with either an atonic or a spastic colon. Time-lapse cineradiography has characterised four patterns:

1. *Constipation with normal transit time:* In these subjects constipation is related to a low fibre diet, minor unclear disturbances in defecation function, and/or psychological disturbances.
2. *Constipation with colonic inertia:* In these subjects there is a delay in the transit of markers throughout the colon. This pattern is found in idiopathic constipation, with systemic disease and with the use of certain medication (Table 13.4).
3. *Constipation with hindgut inertia:* Patients in this group have a segmental slow transit in the descending colon.
4. *Constipation with outlet inertia:* In these subjects there is a delay in passage through the rectosigmoid colon due to the sustained contraction of the internal or external anal sphincter, for example, local causes, Hirschsprung's disease.

There is an epidemiologic association between low dietary fibre intake, constipation, diverticular disease and colorectal cancer.

Clinical evaluation A detailed history is essential to determine what the patient means by 'constipation' and to ascertain the nature of his diet, fluid intake, level of physical exercise and other physical and psychological factors that are known to affect colonic motility.

A history of drug intake is essential as several drugs such as analgesics, antacids (those containing calcium-aluminium), anticholinergics and antidepressants have constipating side effects. Inspection of the stool is informative, especially in the young. Small ribbon-like stools suggest anal stenosis, a large stool suggests rectal inertia, and small hard pellet-like stools suggest a metabolic or dietary cause. Blood mixed with stools suggests a local colonic lesion until proved otherwise. Hemorrhoidal bleeding occurs mainly as 'splashes on the pan'. Anal or rectal pain indicates a local lesion. Spurious diarrhea with blood and mucous may accompany proctosigmoiditis or a colonic neoplasm. A recent change in bowel habits in an elderly person must strongly suggest the latter possibility. Abdominal pain which is relieved by defecation is often seen in irritable bowel syndrome and diverticular disease. The presence of anorexia, weight loss and malaise suggest organic disease though they may be part of a depressive condition too. A detailed history for

Table 13.4 Causes of constipation

1. Idiopathic
2. Irritable bowel syndrome
3. Pregnancy
4. Depression
5. Structural abnormalities
   - Anal fissure
   - Neoplasm (colorectal)
   - Hirschsprung's disease
6. Neurogenic disorders
   - Motor neuron disease
   - Cerebrovascular accident
   - Parkinson's disease
   - Multiple sclerosis
   - Spinal cord injuries
7. Systemic-metabolic disorders
   - Diabetes mellitus
   - Hypothyroidism
   - Hyperparathyroidism
8. Drugs: antacids, antidepressants, anticholinergics, calcium channel blockers

evidence of both hypothyroidism and depression must be sought as both conditions can masquerade as troublesome constipation.

The physical examination of the subject with constipation must include palpation of the abdomen, inspection of the anal region, digital rectal examination and sigmoidoscopy. Abdominal examination may reveal a mass suggesting a neoplasm. It may also reveal palpable fecoliths or the palpable sigmoid and descending colon of irritable bowel syndrome or diverticulosis. Local anal examination may lead to the discovery of an anal fissure or fistula. The tone of the rectal sphincter can be assessed digitally. Sigmoidoscopy is essential to detect proctosigmoiditis, or an underlying neoplasm (which is often within the reach of the sigmoidoscope).

Management Treatment should consist of an explanation of the varying individual frequencies of defecation, stressing the need for consuming large quantities of fluids, fruits and vegetables, and adopting a daily routine of physical activity.

Fibre in the diet can be increased as a remedial measure. Dietary fibre increases stool weight, increases stool water content, accelerates colonic transit and decreases intraluminal pressures in the colon.

Laxative agents may be used for disabling constipation. Bulk laxatives are the preferred class of agents.

APPROACH TO A PATIENT WITH ASCITES

Ascites is defined as the accumulation of fluid in the peritoneal space.

Pathophysiology Ascites forms when the rate of formation of lymphatic fluid exceeds its removal from the peritoneal cavity. Ascitic fluid may be derived from either the surface of the liver or the intestines; in patients with hepatic cirrhosis most of the fluid seeps out of the surface of the liver.

The hepatic sinusoidal system is unique in that the normal sinusoidal pressure is very low, approximately 2 mmHg. This is primarily because of a high ratio of presinusoidal to post-sinusoidal resistance of 50:1. The normal ratio of precapillary to postcapillary resistance is 5:1 in the systemic circulation; intracapillary pressures in the muscles may be 20 mmHg.

An increase in sinusoidal pressure (due to partial venous outflow block, distortion by regenerating cirrhotic nodules or by raised venous pressure) leads to a marked increase in the transudation of lymph. As the hepatic sinusoid is freely permeable to protein, there is no oncotic gradient across the sinusoid. Fluid transudation is therefore influenced mainly by hydrostatic forces rather than by serum protein concentrations. The splanchnic capillaries are also a source of ascitic fluid but their contribution is comparatively less.

The *'underfill' theory* of ascites suggests that the triggering event in ascites formation is the accumulation of peritoneal lymph; this leads to a reduction in intravascular volume, which in turn triggers salt and water retention by the kidneys in an attempt to restore plasma volume.

The *'overflow' hypothesis* suggests that the initiating event in the development of ascites is the inappropriate retention of salt and water by the kidneys. This results in plasma volume expansion and hypervolemia-induced altered Starling forces, leading to ascites.

The two theories are in fact not mutually exclusive. Low pressure hepatic baroreceptors which are sensitive to intrasinusoidal pressure and modulate renal sodium excretion have been now identified and this helps tie up the two theories.

Diagnosis and investigations Whereas severe ascites is readily diagnosed, mild ascites can be diagnosed with proper elicitation of diagnostic signs. The *'puddle sign'* or central abdominal dullness in the 'all fours' position, is a useful sign of early ascites. The causes of ascites are shown in Table 13.5.

Table 13.5 Causes of ascites

1. Hepatic (transudate)
Cirrhosis
Venous outflow obstruction
Hepatocellular failure
2. Cardiac (transudate)
Constrictive pericarditis
Congestive heart failure
(including restrictive cardiomyopathy)
Tricuspid valve disease
3. Malignant (exudate, hemorrhagic)
Lymphoma
Peritoneal carcinomatosis
4. Infectious (exudate, lymphocytic predominance)
Tubercular peritonitis
5. Pancreatic (exudate, high amylase)
Leakage from pseudocyst
Ruptured duct
6. Miscellaneous
Nephrotic syndrome
Chronic renal insufficiency
Meigs syndrome (ovarian fibroma)
Lymphatic telangiectasia

The general physical examination should include a search for signs of chronic liver disease (see next section) which may suggest the presence of portal hypertension, and evidence of any visceral malignancy (supraclavicular lymph nodes). The presence of an elevated jugular venous pressure directs attention to the possibility of right-sided cardiac failure with ascites due to raised systemic venous pressure. Examination of the abdomen should include palpation for any organomegaly. A palpable spleen may indicate portal hypertension; if concomitantly a soft liver is palpable, the likely cause is extrahepatic portal venous obstruction, whereas if the liver is firm or impalpable, cirrhosis is likely. Abdominal tenderness in a patient with ascites due to cirrhosis raises the additional possibility of an infective complication — *spontaneous bacterial peritonitis*. The palpation of a hard nodular liver suggests the likelihood of a liver infiltrated by tumour. A pulsatile liver suggests tricuspid valve disease; pulsations are systolic in tricuspid regurgitation and presystolic in tricuspid stenosis. A periumbilical nodule may be palpable[1] and directs attention to the possibility of metastatic disease with peritoneal seeding. If abdominal collateral veins are prominent, the direction of flow should be noted; flow away from the umbilicus suggest portal hypertension, flow from above downwards towards the umbilicus suggests superior vena caval obstruction, and flow from below upwards towards the umbilicus suggests inferior vena cava obstruction. A pelvic and rectal examination is mandatory in every case of ascites to exclude primaries arising from these sites.

Diagnostic paracentesis (50–100 ml) should be performed and the ascitic fluid obtained should be subjected to biochemical, microbiologic and cytologic analysis and cultures. Transudative ascites is characterised by an ascitic fluid protein content of less than 25 g/l and a specific gravity of less than 1.016; the difference between plasma albumin and ascitic fluid albumin is more than 1.1 g/dl and the cell count is less than 250/μl with a predominance of mesothelial cells. Hepatic, cardiac and renal causes are typically associated with transudative ascites. Ovarian fibromas are also associated with transudative ascites and hydrothorax (Meig syndrome). Exudative ascites typically has a higher protein content (>25 g/l with plasma and ascitic fluid albumin difference less than 1.1 g/dl) and a higher specific gravity (>1.016). The cell count is usually more than 1000/μl and the fluid may be hemorrhagic. Tuberculosis, pancreatitis and malignancies are associated with exudative ascites. Tubercular ascites is straw-coloured and more than 70 per cent of the cells are lymphocytes. Rarely, the ascites may be milky or *chylous*. The causes of chylous ascites include trauma, tuberculosis, filariasis, tumour (lymphomas), congenital anomaly of the lymphatic channels (lymphangiectasia), or rarely, nephrotic syndrome. Chylous ascitic fluid has a high triglyceride content (>1000 mg/dl). When the fluid is milky but the triglyceride

[1] Sister Mary Joseph's nodule

content is low, *pseudochylous ascites* should be suspected; it is due to tumour cells or a very high white cell count in the fluid. Very rarely, ascitic fluid may be mucinous; this indicates seeding by a colloid carcinoma of the stomach or colon, or a rare condition known as *pseudomyxoma peritonei*.[1] Besides ascitic fluid examination, other helpful tests include liver function tests and abdominal sonography. An abdominal ultrasound helps evaluate portal vein patency, liver and splenic englargement and detection of any other visceral or pelvic masses.

Treatment Mild to moderate ascites requires no treatment. However, tense ascites which causes discomfort, respiratory embarrassment or limitation of physical activity is an indication for treatment.

Dietary sodium restriction and diuretics are the mainstay of treatment. Diuretics reduce ascites by reducing intravascular volume; the reduction in intravascular volume is made up by reabsorption of ascitic fluid. Since the maximum rate of this reabsorption is about 400–500 ml/day, a daily weight loss of 400 g is desirable. Loss of weight at a faster rate can result in hypovolemia with consequent renal hypoperfusion.

The diuretic of choice is spironolactone rather than a loop diuretic like furosemide; this is because hyperaldosteronism leads to brisk reabsorption of sodium in the distal tubule, a phenomenon antagonised by spironolactone but unaffected by furosemide.

Paracentesis can be used for symptomatic relief. In the presence of peripheral edema, upto a litre of fluid can be readily removed at a time, without the risk of precipitating hypovolemia.

In every case of ascites, therapeutic measures must be directed at the underlying cause.

[1] Accumulation of encysted yellow, jelly-like material due to an ovarian pseudomucinous cystadenomå or a ruptured mucocele of the appendix

APPROACH TO A PATIENT WITH JAUNDICE

Jaundice (icterus) is the visible accumulation of excess bilirubin in the skin, mucous membranes or sclera, imparting a distinct yellow discolouration to these tissues. Other causes of yellow discolouration of the skin include *carotenemia* (for example, due to the excessive ingestion of carrots), consumption of foods rich in *lycopene* (tomato juice), and *drugs* such as atabrine (antimalarial) or busulfan. Jaundice is usually visible when serum bilirubin levels are more than 2.5 mg/dl.

Etiology The causes of jaundice are listed in Table 13.6.

Clinical approach The history often yields important clues to the etiology of jaundice. Onset with a prodrome of malaise, anorexia and mild fever suggests viral hepatitis. A history of transfusions, injections, tattooing or needle-stick exposure could suggest a parenterally transmitted form of viral hepatitis. Intake of alcohol in excess may suggest a possibility of

Table 13.6 Causes of jaundice

Unconjugated hyperbilirubinemia
1. Overproduction (prehepatic)
Hemolysis
Ineffective erythropoiesis
2. Decreased uptake
Gilbert syndrome
Crigler-Najjar syndrome
Sepsis
Conjugated hyperbilirubinemia
1. Impaired hepatic excretion
Familial disorders (Dubin-Johnson syndrome)
Hepatocellular disease (hepatitis)
Drugs
Sepsis
Primary biliary cirrhosis
Postoperative
2. Extrahepatic obstruction
Cholelithiasis / choledocholithiasis
Tumours of the pancreas, bile ducts, gallbladder
Biliary strictures

alcoholic hepatitis. The patient must be asked about the possible intake of any hepatotoxic drug in the recent past. A family history of jaundice may be a clue to Wilson's disease or to one of the hereditary hyperbilirubinemias. The patient's ethnic background and a history of recent intake of an offending drug may point to a hemolytic anemia due to deficiency of the enzyme glucose-6-phosphate dehydrogenase in the erythrocytes. High grade fever with jaundice should lead to a search for a source of sepsis, such as cholangitis or hepatic abscess.

The colour of urine is an important point in the history. Normal-coloured urine in the presence of jaundice indicates an unconjugated hyperbilirubinemia. Dark urine implies conjugated hyperbilirubinemia. The presence of anorexia and significant weight loss, especially in

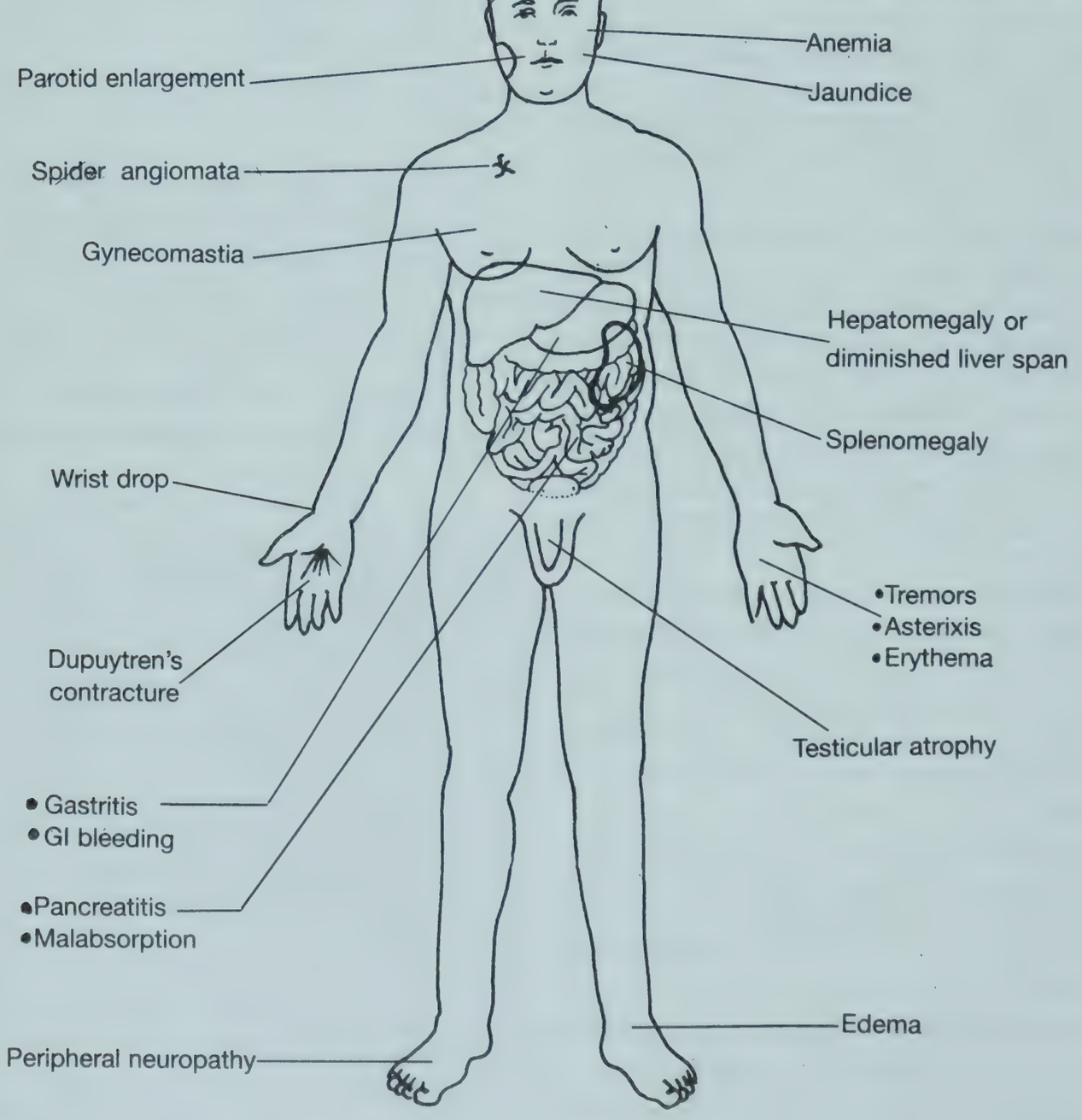
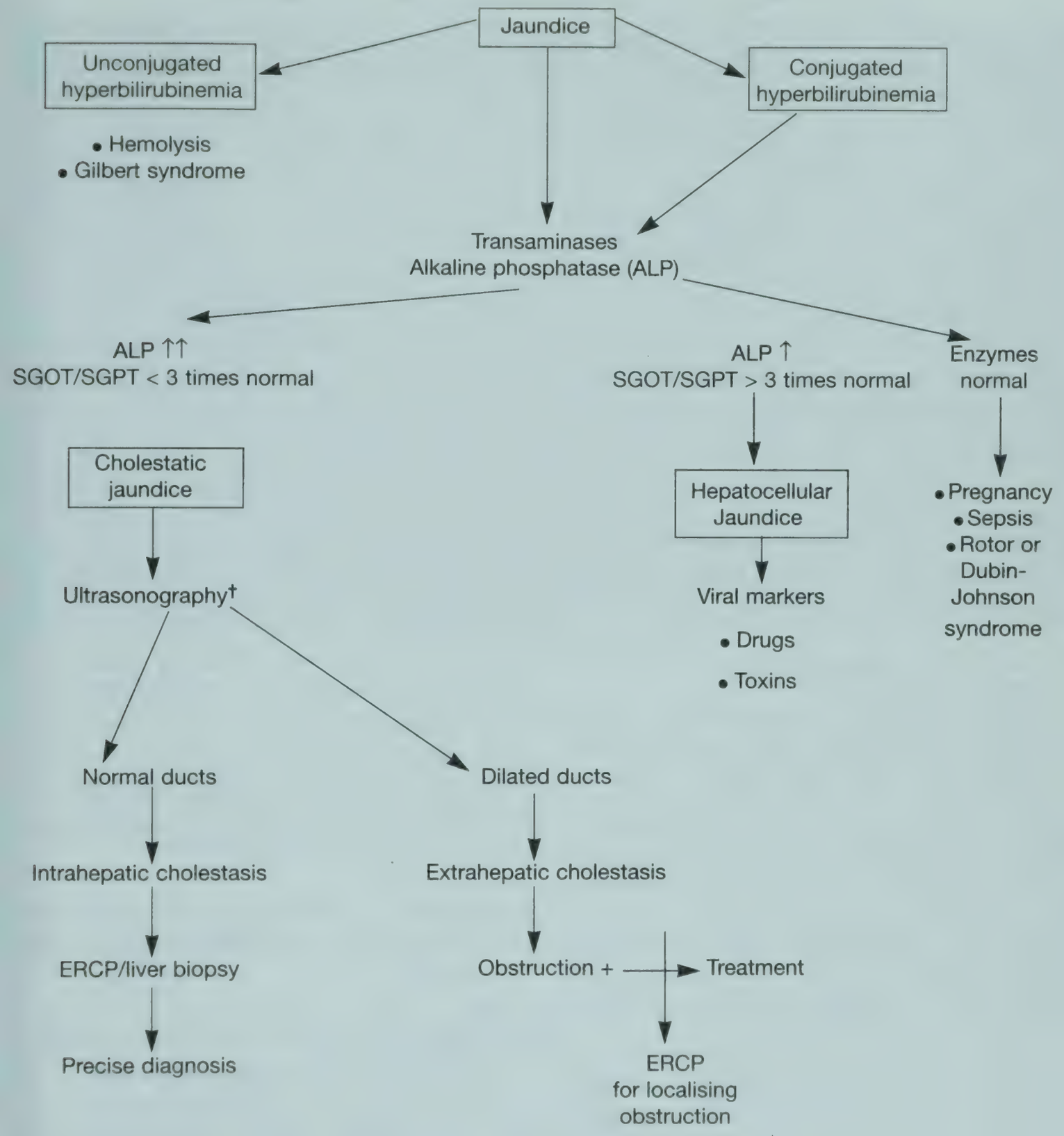


Fig 13.2 Stigmata of chronic liver disease



† CT may be used too; it is more expensive but is better for detecting stones within non-dilated ducts.

Fig 13.3 Investigation of jaundice

Table 13.7 Differences between medical and surgical causes of cholestatic jaundice

	Intrahepatic cholestatic (medical) jaundice	*Extrahepatic cholestatic (surgical) jaundice*
History	contact prodromal illness blood transfusion drugs	dyspeptic symptoms previous episodes
Pain	mild/absent	present/severe may be colicky
Fever	usually low grade, short duration during prodrome	high grade fever suggests cholangitis
Palpable liver		
size	< 5 cm	> 5 cm
nodularity	–	+ if metastatic disease
Palpable spleen	may be present	absent
Palpable gallbladder	absent	may be present
Ascites	±	present, if there is malignant obstruction
Liver function tests		
bilirubin	may be very high	usually<10 mg/dl
ALP	< 30 King Armstrong units	>30 K.A. units
SGOT/SGPT	elevated > 5 x normal levels	< 5 x normal levels

an elderly patient, must prompt the search for an underlying malignancy.

A careful physical examination is often rewarding. A meticulous search must be made for 'stigmata of chronic liver disease' (Fig 13.2). These include spider nevi, palmar erythema, digital clubbing, white nails, gynecomastia, testicular atrophy, loss of body hair (in males), prominent abdominal veins and, in alcoholic liver disease, parotid enlargement and Dupuytren's contracture. Skin excoriations indicate cholestasis. The cornea must be examined for a Kayser-Fleischer ring (Wilson's disease).

The liver is palpated and the liver span determined (the normal span is 11–14 cm). Tenderness of the liver indicates some pathology but does not discriminate among the various causes. Intercostal tenderness is seen classically in an amebic liver abscess. While a 'just' palpable spleen is common in several acute hepatic conditions, significantly large splenomegaly may indicate underlying portal hypertension or a hemolytic anemia.

A palpable gallbladder which is tender may indicate acute cholecystitis. A palpable non-tender gallbladder indicates distal obstruction either by a neoplasm (formerly called the *Courvoisier law*) or by an impacted gallstone. A firm mass in the gallbladder area may indicate carcinoma of the gallbladder.

Investigations Investigations are outlined in the self-explanatory algorithm in Fig 13.3 and Table 13.7.

APPROACH TO A PATIENT WITH UPPER GASTROINTESTINAL BLEEDING

Hematemesis refers to the vomiting of red blood or 'coffee ground' material and signifies a source of bleeding in the esophagus, stomach or the duodenum, proximal to the ligament of Treitz. Black tarry stools (melena) indicate a slower rate of bleeding from the upper gastrointestinal tract.

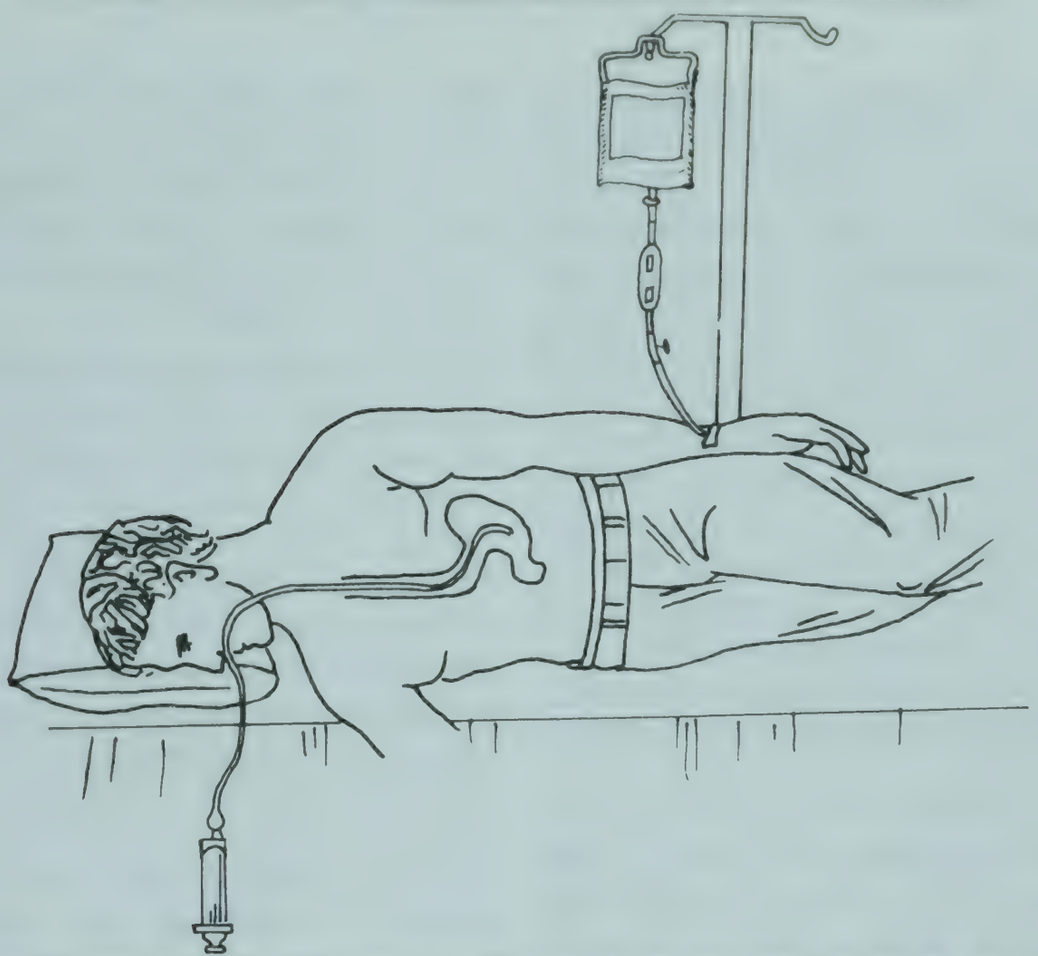


Fig 13.4 Nasogastric lavage: a. Perform lavage using either room temperature or iced saline solution or antacid; b. Remove the clots and intragastric material; c. If the nasogastric aspirate is clear or clears promptly with lavage, the tube may be removed

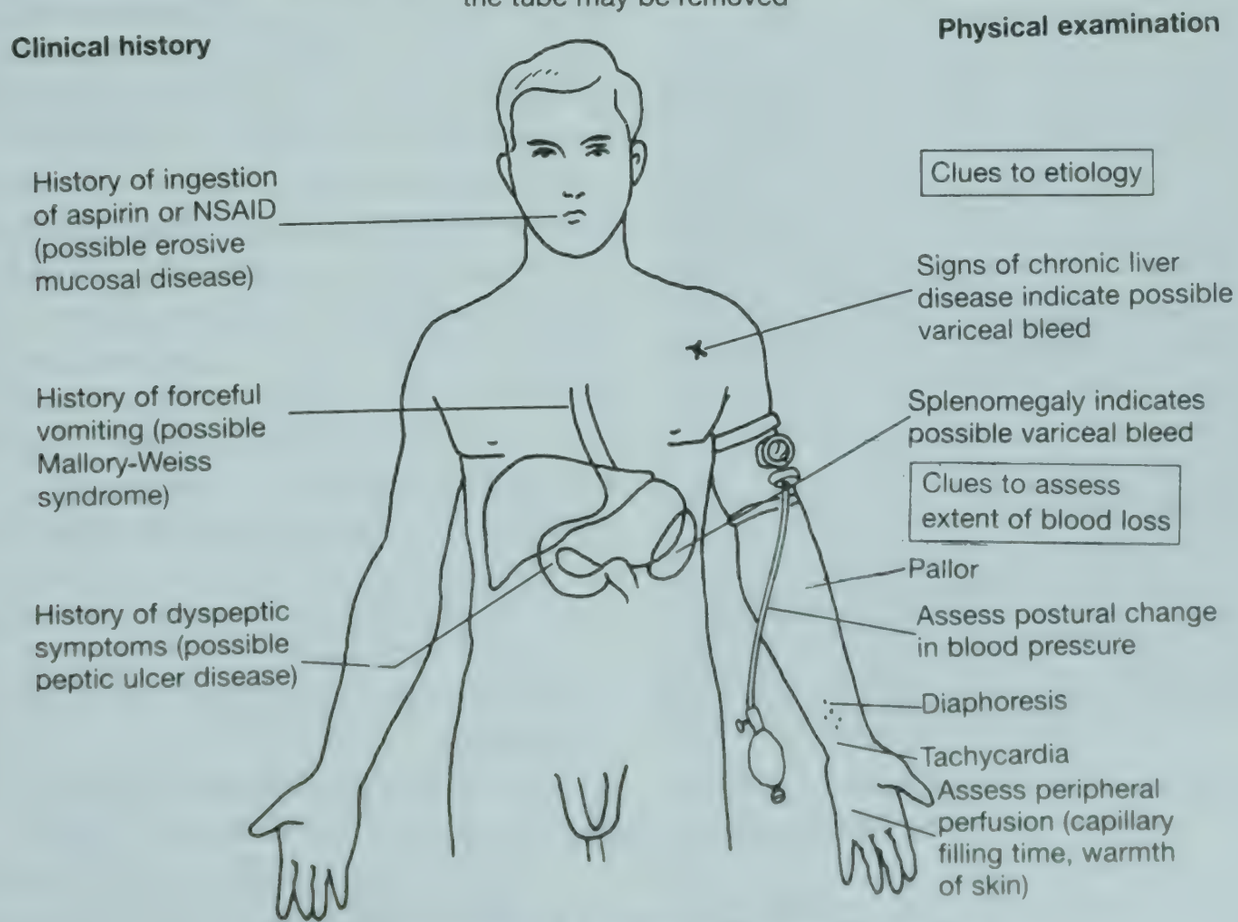


Fig 13.5 Examination of a patient with upper GI bleeding

Pathophysiology and etiology The causes of upper gastrointestinal bleeding are listed in Table 13.8.

Loss of blood into the gastrointestinal tract results in hypovolemia with a consequent reduction in venous return. This results in compensatory tachycardia and generalised vasoconstriction. Systemic hypotension results when the blood loss exceeds 20 per cent of blood volume (1500 ml). The hemoglobin then drops, often to below 8 g/dl, the resting pulse rate exceeds 120 b.p.m. and rises by 20 b.p.m. on sitting up. The systolic blood pressure drops to 100 mmHg and there is a postural fall of 20/10 mmHg (systolic/diastolic) on sitting up. All these signs indicate a massive gastrointestinal bleed.

In one study in north India, the commonest cause of upper gastrointestinal bleeding was variceal bleeding (50%) followed in frequency by erosive mucosal disease (20%) and peptic ulcer disease (20%).

Table 13.8 Causes of upper GI hemorrhage

Common causes
Esophageal varices
Peptic ulcer disease
Erosive mucosal disease
Uncommon causes
Neoplasms
carcinoma stomach
carcinoma esophagus, duodenum
gastric lymphoma
Mallory-Weiss syndrome
Vascular
hereditary telangiectasia
aortic aneurysm
pseudoxanthoma elasticum
coagulopathies
hemobilia
pseudocyst of the pancreas

Clinical approach and management The three steps in the management of upper gastrointestinal bleeding are:

Step 1 : resuscitation of the patient by restoring blood volume

Step 2 : diagnosing the cause of the bleeding and directing treatment towards control of the bleeding lesion

Step 3 : triage of patients into low and high risk by identifying the patients at risk of rebleeding

Step 1 : Resuscitation of the patient is begun immediately on her arrival at the emergency services. After clinical assessment and recording vital signs, the amount of blood lost is often evident. Two intravenous access lines are inserted and blood samples sent for grouping, cross-matching and other laboratory investigations including hemoglobin, hematocrit, platelet count, prothrombin time, BUN and serum electrolytes. Infusion of a crystalloid solution (saline or dextrose) is begun immediately through both accesses and blood transfusion begun through one of them once blood is available. A large-bore (16F) nasogastric tube is inserted and the stomach is lavaged with room temperature saline or water. Irrigation of the stomach helps assess rapidity of bleeding, clears blood (permitting endoscopy) and decreases the gastrointestinal protein load. The use of iced saline or levarterenol for lavage is of no additional benefit. The nasogastric tube should be removed after diagnostic aspiration; prolonged use is associated with risks of mucosal damage, aspiration and reflux esophagitis. If the initial aspirate is clear, the nasogastric tube should be left in place for a few hours; this is done because active duodenal bleeding can occur with an initially clear aspirate.

The end point of resuscitative measures include

a. disappearance of signs of cutaneous vasoconstriction,
b. the return of pulse and blood pressure to normal,
c. a urine output stable at 30 ml/hour,
d. a hematocrit maintained at 30–35%, and
e. a central venous pressure of 8–15 cm H_2O (if a CVP line has been inserted to guide fluid replacement).

ep 2: While the patient is being resuscitated e clinical examination is completed (Fig 13.5). ecifically stigmata of chronic liver disease letailed in the section on jaundice) are looked r. The most important clue on physical xamination is a palpable spleen that often dicates a variceal origin of hemorrhage. Rarely a patient encountered who has variceal emorrhage but has no splenomegaly. Also, in dia unlike in the West, most patients with ortal hypertension bleed only from the varices. is essential to elicit a history of dyspeptic mptoms existing for more than four weeks as it ints to a likelihood of a bleeding peptic ulcer the underlying etiology of gastrointestinal eeding. A history of recent intake of drugs like spirin or other non-steroidal antiinflammatory ugs or alcohol may indicate erosive mucosal sease as the underlying cause. It must, owever, be borne in mind that 50 per cent of atients with a bleeding peptic ulcer have a story of drug intake as well.

ep 3: This involves the triage of patients into w and high risk subsets. The low risk group can e discharged for treatment at home and cludes subjects with the following haracteristics:

- non-variceal bleed, age of patient less than 40 years;
- melena alone, no dyspeptic symptoms, clear nasogastric aspirate;
- pulse rate less than 100 bpm and systolic BP, more than 100 mmHg.

High risk patients require immediate ospitalisation for further treatment and include bjects with the following characteristics:

- likely variceal bleed, age of patient more than 40 years;
- hematemesis, presence of dyspeptic symptoms for four weeks, pink/brown nasogastric aspirate;
- pulse rate greater than 100 b.p.m and systolic BP less than 100 mmHg

In high risk patients, a diagnostic endoscopy is dicated. It is preferably done in all patients and during the acute bleeding episode since the source of blood loss can be detected only in the acute stage. Endoscopy is diagnostic in variceal hemorrhage and erosive mucosal disease. It not only establishes the diagnosis of a bleeding peptic ulcer but is also of prognostic value in this subset. The presence of a fresh clot, a visible vessel in the ulcer crater (known as the *visible vessel sign*) especially if it is spurting, or of a darkened slough in the ulcer, all indicate a high likelihood of recurrence of bleeding. Endoscopy is also therapeutic in variceal bleeding, because it facilitates endoscopic sclerotherapy (EST), that is, endoscopic injection of a sclerosant like 5 per cent ethanolamine or polydecanol into the bleeding vessel. Endoscopic band ligation is also very effective.

Other therapeutic measures in upper GI hemorrhage

Infusion of vasoconstrictors: Several vasoconstrictors can be infused intravenously to stop bleeding from the culprit vessel. These include somatostatin or its analogues like octreotide, and vasopressin (dosage 0.2 units per minute for 24 hours, with a watch for arrhythmias and overhydration).

Sengstaken-Blakemore tube: This double balloon triple-lumen tube was earlier used often to control variceal bleeding when sclerotherapy was not available. It has one lumen for aspirating gastric contents, and two others for inflating the gastric and esophageal balloons. It relies on arresting bleeding by mechanical tamponade. Though it controls bleeding in 90 per cent of patients, it has to be deflated after 24–36 hours whereupon there is a very high relapse rate of bleeding (70 per cent). Pressure necrosis of the cardia occurs in almost all patients though it may be clinically significant in fewer subjects.

Electrocoagulation, laser coagulation, autologues, clot embolisation, stapling with a staple gun: These measures are costly, difficult to perform by an untrained individual and therefore, less practicable.

Antacids (high dose) and H_2 receptor antagonists: These agents have a central role in bleeding ulcers and in erosive mucosal disease. Antacids raise gastric pH and thus help in coagulation besides preventing clot lysis. H_2 receptor antagonists decrease acid secretion.

Surgery in upper GI bleed: The indications and the types of procedures are shown in Table 13.9.

LOWER GASTROINTESTINAL BLEEDING

A bleeding source in the jejunum, ileum, large bowel or rectum (distal to the ligament of Treitz) results in lower gastrointestinal bleeding. *Hematochezia* refers to the passage of bright red blood per rectum. It is to be remembered that the colour of stools does not always correlate well with the site of bleeding. Intestinal transit time is a key factor. Thus rapid upper gastrointestinal bleeding with a short transit time can result in hematochezia. Lower gastrointestinal bleeding with a prolonged transit time, conversely, can result in dark-coloured stools (melena).

Etiology and pathophysiology The causes of lower gastrointestinal bleeding are shown in Fig 13.6 and Table 13.10.

The pathophysiology of lower gastro intestinal bleeding is similar to that of uppe gastrointestinal bleeding. The amount of bloo loss, the age of the patient and the presence o absence of complicating factors like underlyin vascular disease or anemia, dictate th hemodynamic response of the individual. Th assessment of the amount of blood lost is simila to that for an episode of upper gastrointestina bleed.

Clinical approach and management The tw principal steps in the management of an episod of lower gastrointestinal bleeding ar resuscitation (Step I) and diagnosis an definitive management (Step II).

Step 1: *Resuscitation*: The general principle are similar to those for upper gastrointestina bleeding, that is, replacement of blood volum (by blood and colloids) and maintenance of vita signs.

Step 2: *Management*: This involve establishing a diagnosis and is simpler whe compared to the strategies for uppe gastrointestinal bleeding (Fig 13.7). The age o the patient assumes considerable importance. I adolescents and young individuals, Meckel diverticulum is an important cause of bleedin whereas in the elderly ischemic colitis angiodysplasia of the colon and colonic polyp

Table 13.9 Surgery in upper GI bleeding

Underlying cause	*Indication for surgery*	*Procedure*
1. Ulcer	1. Continuous bleeding requiring >5 units transfusion/24 hrs 2. Rebleeding (massive) 3. Perforation + bleeding 4. Rare blood group or shortage of blood	A. **Gastric ulcer** Billroth I gastrectomy B. **Duodenal ulcer** Truncal vagotomy + Pyloroplasty + Underrunning of ulcer
2. Varices	1. Failure of initial therapy 2. Rebleeding after admission	Emergency Lienorenal shunt
3. Erosive mucosal disease	1. Massive bleeding (2000 ml/24 hrs) 2. Rare blood group	Truncal vagotomy + Antrectomy

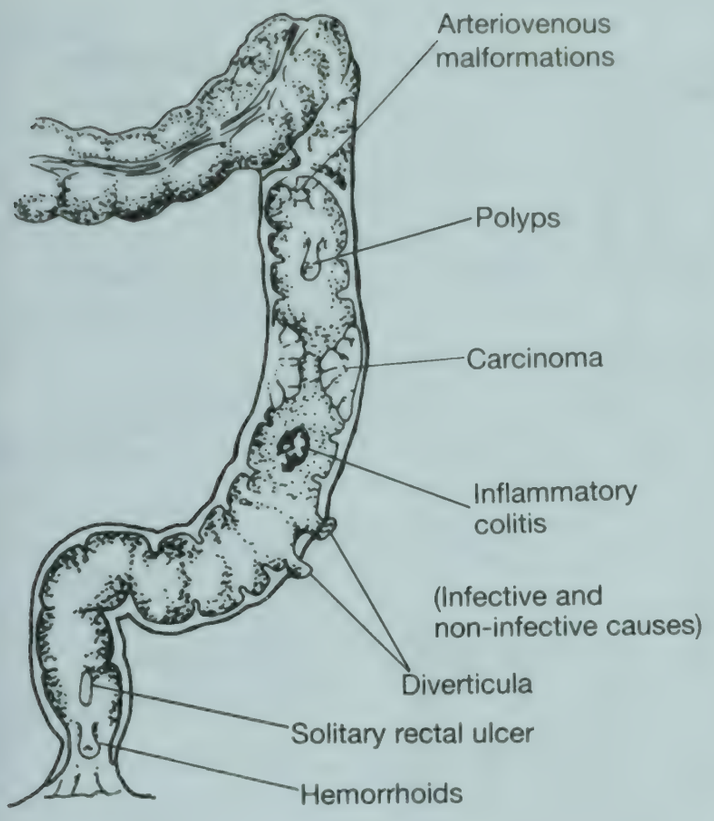


Fig 13.6 Cause of lower gastrointestinal bleeding

Table 13.10 Causes of lower gastrointestinal hemorrhage

Common causes
Inflammatory bowel disease
Colonic polyp
Meckel's diverticulum
Carcinoma of colon
Angiodysplasia of colon
Uncommon causes
Diverticular disease *
Infective enterocolitis
Ischemic infarction of small or large bowel
Hereditary telangiectasia
Solitary rectal ulcer
Hemorrhoids
* commonest cause in the West

are important causes. Inflammatory bowel disease is an important cause of lower gastrointestinal hemorrhage in middle-aged individuals. Infective enterocolitis is an important cause in all age groups especially in conditions where there is a lack of proper hygiene, sanitation or a clean source of water supply. Unlike in the 'developed' countries, diverticulosis is rare in India, possibly due to the high fibre content in the diet.

The physical examination must include a search for the stigmata of inflammatory bowel disease or bleeding lesions like telangiectasia, and for valvular aortic stenosis (associated with angiodysplasia). Very often the physical examination may not be contributory. A per rectum digital examination to exclude a neoplasm is important; 25 per cent of colonic malignancies are within the reach of a finger.

A *proctosigmoidoscopy* is next in the order of importance, provided of course that a stool examination has already been carried out to rule out infective colitis. The presence of fecal leukocytes or a pathogen like the trophozoites of *Entameba histolytica* indicate infective colitis. A rigid sigmoidoscope is preferable to a fibreoptic one when there is ongoing bleeding because blood may hinder observation with a fibreoptic endoscope besides blocking the bowel lumen. An inflamed colon is seen in both infective as well as in inflammatory bowel disease, and the gross appearance itself may not be discriminatory.

A normal proctosigmoidoscopy may be followed up with a colonoscopy, provided the bleeding is not brisk. Brisk bleeding necessitates further investigation, either in the form of radionuclide scintiscanning with radiolabelled technetium-99m tagged RBCs injected intravenously, or by angiography.

When the rate of blood loss is at least 5–6 ml/minute, the bleeding site can be identified by a 'flush' abdominal aortogram. A rate of blood loss of 0.5–1 ml/minute may necessitate selective arteriography; selective arteriography of the inferior mesenteric artery is done before that of the superior mesenteric artery, the latter being undertaken only if no

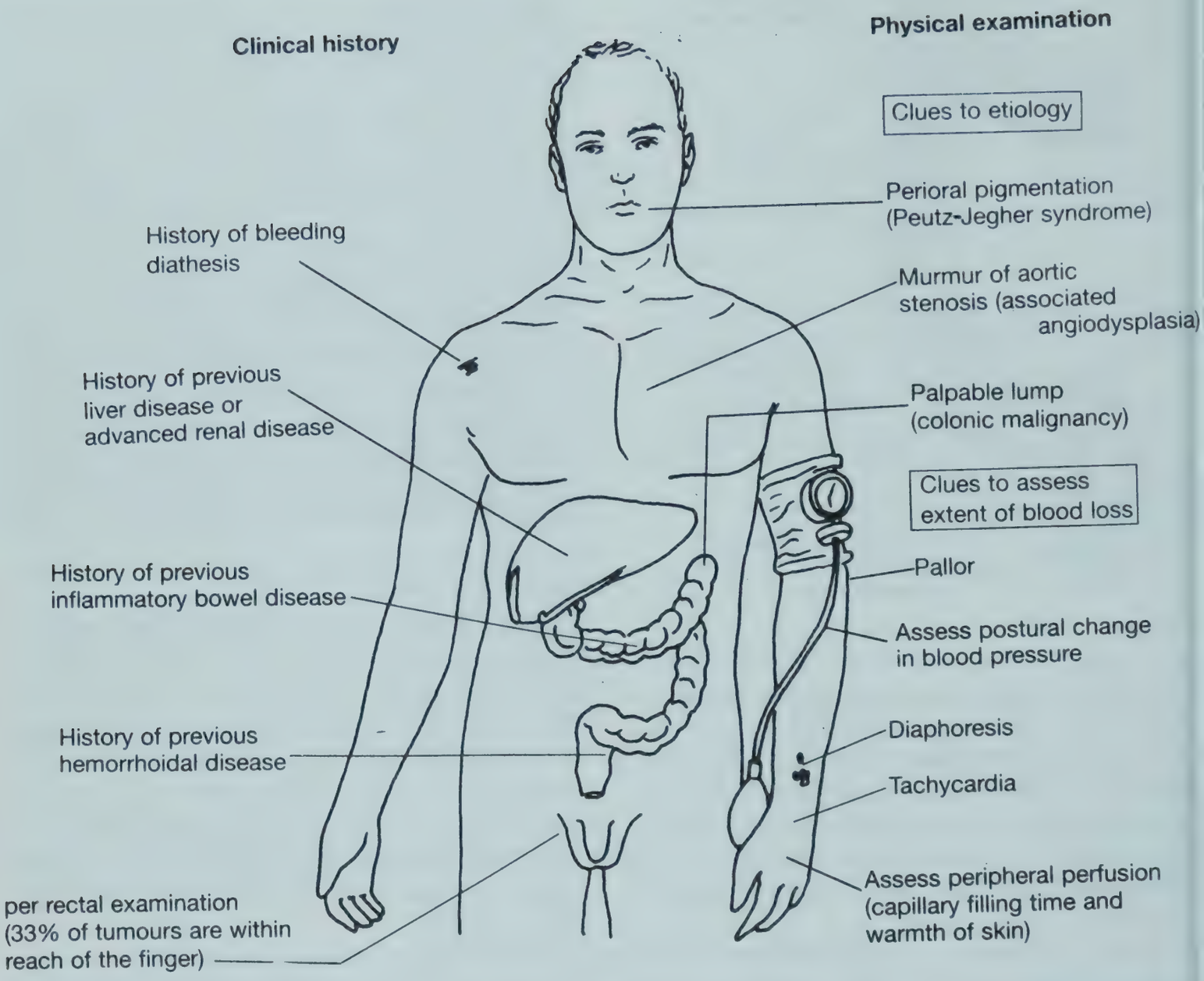


Fig 13.7 Examination of patient with lower GI bleeding

leakage is identified in the former angiogram. The angiogram clearly indicates the site and vascular source of the bleeding which is evident as extravasation of contrast which persists into the capillary phase. The absence of filling of the portal vein in the venous phase may signify bleeding from the varices.

Specific therapy Specific antiinfective agents for infective colitis, antiinflammatory agents for inflammatory colitis and (endoscopic) polypectomy for bleeding polyps are some of the specific measures. When the cause is obscure and angiography reveals a leak, a segmental resection of the diseased segment is rewarding. When the angiography is non-contributory or non-available, blind right-hemicolectomy results in cessation of the lower gastrointestinal bleed in most of the obscure cases.

KEY CONCEPTS

Dysphagia

- Dysphagia may be due to a *mechanical* cause (luminal narrowing) or may result from a *motor* disorder (motility disturbance).
- Mechanical causes of dysphagia include esophageal strictures, rings or tumours. Causes of esophageal dysmotility include pharyngeal paralysis, achalasia, progressive systemic sclerosis and diffuse esophageal spasm.
- A detailed history can provide important clues to the etiology. When dysphagia for liquids precedes that for solids, a motility disorder may be likely. Dysphagia of a long duration suggests a benign etiology. Occasionally, the patient is able to indicate the site of the lesion by pointing out where the food gets 'stuck'. A detailed neurologic examination serves to exclude a neurologic cause of dysphagia.
- Important investigations include a barium swallow with cineradiography, endoscopy and esophageal motility studies.

Diarrhea

- Diarrhea refers to the passage of loose stools (>300g per day). Diarrhea may be *acute* (<2 weeks duration; usually due to infections) or *chronic* (duration >2–3 weeks; common causes include irritable bowel syndrome, chronic parasitoses [e.g giardiasis], malabsorption syndrome, inflammatory bowel disease).
- It is also useful to differentiate between *small bowel* diarrhea (large volume stools, watery consistency, and associated with periumbilical pain) and *large bowel* diarrhea (small volume, semi-formed, with associated tenesmus). It is also important to distinguish *organic* from *functional* diarrhea; a history of nocturnal diarrhea suggests organic disease.
- The investigations in a patient with acute diarrhea includes stool examination for parasites (e.g. methylene blue staining for *E. histolytica*), bacteria (e.g., hanging drop preparation for *Vibrio cholera*) and cells (the presence of polymorphonuclear cells indicates an inflammatory enteritis; this may be infective or it may be due to inflammatory bowel disease). If malabsorption syndrome is suspected, fecal fat content serves as a good screening test. A jejunal biopsy may be contemplated if the index of suspicion of a mucosal disease is very high. An abdominal ultrasonographic examination aids the diagnosis of pancreatic disease.
- The treatment depends on the cause of diarrhea. Opiate agents may be useful in secretory diarrhea, clonidine is effective for diabetic diarrhea while omeprazole is helpful in Zollinger-Ellision syndrome. If the diarrhea is neuroendocrine in origin, phenothiazines may be effective. Indomethacin is useful in diarrhea due to an intestinal villous adenoma. Appropriate antimicrobials are indicated in infective diarrhea (non-viral).

Irritable bowel syndrome

- This is probably the most common GI disorder. Adults are affected more than children and there is a female preponderance. Abnormalities in muscle tone of the GI tract potentiated by emotional (and psychological) factors and dietary fibre deficiency play a role in pathogenesis.
- The principal symptoms include abdominal pain, bloating, and alternating diarrhea and constipation (though one of the two predominates). Passage of mucous (*but not blood*) is a feature.
- Diagnosis is clinical and sigmoidoscopy is normal. Drug therapy includes antispasmodics for pain, and symptomatic treatment of diarrhea and constipation (increasing fibre and avoiding food which exacerbates the condition). Antidepressants may benefit a subset of patients.

Constipation

- Constipation refers to the passage of stools less than three times in a week.
- Constipation may be due to *an increased colonic transit time* (motility disorders, drugs or neurologic disease) or may result from an *obstructing colonic lesion* (e.g., neoplasm).
- Passing small hard stools suggests a metabolic cause of constipation (such as diabetes mellitus, hypothyroidism) while passing large infrequent stools suggests colonic inertia.
- Usually there is no obvious cause which is evident and investigations are seldom helpful.
- The treatment consists of increasing the intake of fluids and dietary fibre (20–30 g/day). Bulk laxatives may be used if constipation is troublesome.

Ascites

- Ascitic fluid may be a *transudate* (<2.5 g/100 ml; specific gravity <1.016) or an *exudate*. The causes of a peritoneal transudate include hepatic cirrhosis, congestive heart failure, renal failure with fluid retention, and hypoalbuminemia. The causes of an exudative ascites include infections (bacterial, with predominant polymorphonuclear cells; tuberculosis: straw-coloured with mononuclear cells), neoplastic infiltration (usually hemorrhagic fluid), pancreatitis (associated with elevated triglyceride content >1000 mg/dl).
- The history and physical examination should seek clues to these potential etiologies. Investigations include obtaining an ascitic tap and sending the fluid for cytologic and chemical analysis. Liver function tests (for evidence of hepatocellular dysfunction),

ultrasonography (for excluding hepatic nodules and for evaluating patency of hepatic venous outflow), cardiac imaging (if congestive heart failure is suspected), abdominal CT (especially if pancreatic ascites is suspected) and peritoneal biopsy (for peritoneal tuberculosis) are important investigative adjuncts.

➢ Treatment depends on the underlying etiology. General measures include dietary salt and fluid restriction, use of diuretics (spironolactone group is advantageous) and parancentesis (up to a litre can be removed at a time if there is evidence of peripheral edema).

Jaundice

➢ Jaundice may be due to hemolysis (*unconjugated* hyperbilirubinemia) or hepatobiliary disease (*conjugated* hyperbilirubinemia associated with dark-coloured urine).

➢ The history and physical examination yield valuable clues to the etiology of jaundice. A history of a *prodromal phase* suggests viral hepatitis whereas a history of *drug* intake may suggest a drug-induced hepatitis. High *fever with rigors* in a jaundiced patient point to the possibility of biliary obstruction with sepsis (cholangitis). Likewise, a *palpable gallbladder* in a jaundiced patient suggests a tumour with distal biliary obstruction (*Courvoisier's law*). The presence of stigmata of chronic liver disease (spider nevi, palmar erythema, gynecomastia, parotid enlargement) must be sought. If ascites or portal hypertension is present, cirrhosis is the likely underlying substrate.

➢ Hemolysis is suggested by unconjugated hyperbilirubinemia with associated findings in the peripheral blood smear (findings depend on the etiology of hemolysis). Unconjugated hyperbilirubinemia, with no evidence of hemolysis and with normal liver function tests suggest a diagnosis of Gilbert syndrome. Liver function tests help in distinguishing between intrahepatic (medical) and extrahepatic (surgical) cholestasis. A *greater than* threefold elevation of transaminases is *suggestive of hepatitis;* conversely, a less than threefold elevation of transaminases but *marked elevation of ALP indicates extrahepatic obstruction.*

➢ An ultrasound or a CT scan is invaluable in the diagnostic process. The presence of *dilated extrahepatic biliary ducts suggest extrahepatic obstruction.* An ERCP is useful for evaluating distal biliary obstruction whereas a PTC may be useful in delineating proximal obstruction within the biliary tree.

Upper GI bleeding

➢ Upper GI bleeding refers to bleeding from a source proximal to the ligament of Treitz. It may be brisk when it appears as *hematemesis* (vomiting bright red blood or coffee-colored contents) or slow when it appears as *melena* (black tarry stools).

➢ Hematemesis must be distinguished from hemoptysis.

➢ The three most common causes of an upper GI bleed are esophageal varices, peptic ulcer disease and erosive mucosal disease.

➢ When evaluating a patient with an upper GI bleed, the initial step consists of *resuscitation* (assess degree of blood loss; orthostatic change in blood pressure and heart rate indicate significant loss) with volume (and blood) replacement

➢ The next step is to *identify the etiology* of the bleeding. The presence of a palpable spleen generally suggests portal hypertension with a likely variceal bleed. A history of dyspeptic symptoms favours diagnosis of a bleeding peptic ulcer. A history of drug intake may suggest erosive mucosal disease as the probable cause of bleeding. An emergency endoscopy is usually required for identifying the cause of bleeding.

➢ The third step is to *identify patients who merit hospitalisation.* The age factor (>40 years), a likely variceal source of bleeding or the presence of orthostatic changes in BP point to a 'high risk' patient with an increased risk of rebleeding.

➢ The specific treatment depends on the etiology. *Endoscopic sclerotherapy* and variceal banding are effective in variceal bleeding. If these facilities are not available, a Sengstaken-Blakemore tube can provide temporary relief (balloon tamponade of varices). Nasogastric irrigation and H_2 receptor antagonists have a role in bleeding due to peptic ulcer disease or erosive mucosal disease.

Lower GI bleeding

➢ Lower GI bleeding refers to bleeding from a source distal to the ligament of Treitz. *Hematochezia* is passing of bright red-coloured blood in stools and is usually due to a rapid transit time within the gut.

➢ The common causes include inflammatory bowel disease, colonic neoplasm, infective enterocolitis and ischemic colitis (in the elderly). Diverticulosis is an important cause in Europe and America.

➢ The initial step is resuscitation with volume replacement. The presence of orthostatic changes in blood pressure or pulse rate suggests significant blood loss.

➢ Examination of stools may reveal an infective cause (e.g., amebiasis). Digital examination is important since a quarter of rectal neoplasms are within reach of the finger. Proctosigmoidoscopy may be helpful in the diagnosis of inflammatory bowel disease. Arteriography may help localise bleeding (when the rate is 1–2 ml/minute or more). Radiolabelled erythrocytes may help identify an occult source.

➢ The specific treatment depends on the underlying cause.

13.3 Diagnostic methods in gastroenterology

Esophageal Disorders

X-ray

Double contrast studies, in which barium is administered followed by a radiolucent substance such as air, to produce a thin layer of barium coating on the mucosa, are more useful than conventional methods in helping detect various types of lesions, including those confined to the mucosa. Ulcers, strictures and varices can be detected when fluoroscopy with a cinevideo is combined with a barium swallow. Esophageal motility disorders can also be delineated.

Esophageal manometry

Measurement of intraluminal pressure transmitted through fluid-filled, open-tipped catheters (attached to strain gauges) is posssible by passing the assembly into the stomach and gently withdrawing it in steps of 0.5 cm while recording pressures. In this way the pressure in the stomach, and at the lower and upper esophageal sphincters can be measured and the responses to swallowed water can be assessed.

pH determination

Esophageal pH is measured by portable intraluminal electrodes located 5 cm proximal to the lower esophageal sphincter over 24-hour periods. A drop of esophageal pH to 4 signifies reflux of acid.

Bernstein's acid perfusion test

To decide whether the patient's chest pain has an esophageal origin, a tube is passed upto the midesophagus and normal saline/0.1 N. hydrochloric acid infused without the patient's knowledge about the nature of the perfusate. Appearance of symptoms with acid perfusion but not with saline perfusion indicates acid-induced esophageal chest pain.

Gastric Disorders

X-ray

Double contrast barium examination of the stomach is widely used to detect gastric mass lesions, gastric ulcers, duodenal ulcers and erosive gastritis.

Gastric secretory capacity

Since there is a wide overlap in secretory rates between normal people and patients with duodenal and gastric ulcers, gastric secretory studies are of little value in the routine diagnosis of peptic ulcer disease. They may be obtained, however, in subjects suspected to have the Zollinger-Ellison syndrome.

Small Bowel Disorders

Roentgenography

Plain X-ray films are of limited value except for revealing pancreatic calcification (typically overlying or adjacent to the second lumbar vertebra) or evidence of bowel obstruction. Small bowel obstruction is seen as fluid- and gas-filled loops of small intestine with a 'stepladder pattern' of air fluids levels and an absence of colonic gas. Strangulating obstruction, however,

may not have these features and the X-ray film may even be normal. On occasion a coffee bean-shaped strangulating mass and a haze (due to peritoneal fluid) may be evident.

For mucosal diseases barium examination is the procedure of choice. *Enteroclysis* is a specialised barium study wherein barium is infused rapidly into the jejunum through a nasogastric tube.

Quantitative fecal fat

This is the best test for establishing the presence of steatorrhea. Fat is measured in a 72-hour stool collection; the 24-hour content is less than 6 g and the coefficent of fat absorption is greater than 95 per cent. The proportion of fat in the stool (normal is less than 6 per cent) also gives an idea of the etiology of steatorrhea; in pancreatic insufficiency it is generally more than 9.5 per cent, whereas in mucosal disease it is 6–9.5 per cent.

D-xylose absorption

This pentose is relatively well-absorbed but little of it is metabolised so that its urinary excretion or blood levels correlate well with mucosal absorptive efficiency. Thus, after a 25 g oral dose, normally the blood levels two hours later are more than 30 mg/dl and the five-hour urinary excretion is more than 4.5 g. Lower values indicate, most frequently, proximal small bowel mucosal disease.

Schilling test for vitamin B_{12} absorption

This test indicates the absorptive efficiency of the distal ileal mucosa. Normally, oral administration of a radiocobalt-labelled vitamin B_{12} preparation results in urinary excretion of more than 8 per cent over the next 24 hours. An abnormal test may be corrected by a second oral dose of intrinsic factor when it suggests pernicious anemia as a likely etiology, or by a course of antibiotics when it suggests a bacterial overgrowth syndrome. Failure to correct an abnormal Schilling test either reflects mucosal disease or exocrine pancreatic insufficiency.

Breath tests

Breath tests depend upon the measurement of breath excretion of a radiolabelled byproduct of bacterial decompostion of an unabsorbed disaccharide (for example, lactose feeding leading to increased breath hydrogen) or an unabsorbed bile acid (for example cholylglycine feeding leading to increased labelled carbon dioxide). This can happen in mucosal disease as well as in bacterial overgrowth syndromes. Breath urea test is used for diagnosing *Helicobacter pylori* infection.

Mucosal biopsy

Small intestinal mucosal biopsy with a suction biopsy instrument is a safe and definitive means of diagnosing mucosal disease. The biopsy may show *diagnostic changes* in some disease (abetalipoproteinemia, celiac and tropical sprues, agammaglobulinemia, Whipple's disease) and *suggestive changes* in others (lymphangiectasia, amyloidosis, lymphoma).

Disorders of the Pancreas

Serum enzymes

Serum amylase concentrations have been useful in the diagnosis of acute pancreatitis. They rise typically in the first 12 hours and return to normal within 3–4 days. Increased serum amylase is accompanied by increased urinary amylase in pancreatitis (due to an increased renal clearance). The rare benign condition of *macroamylasemia* results from the complexing of amylase with an immunoglobulin, the complex being too large for renal excretion. In this condition also serum amylase levels are raised but urine levels are low or normal. Whereas a level of serum amylase greater than three times normal is almost diagnostic of acute pancreatitis, lesser degrees of elevation can be found in a variety of acute abdominal conditions, such as a perforated viscus, biliary colic or intestinal obstruction.

Fat absorption tests

These have been discussed earlier.

Secretin test

In this test duodenal intubation is undertaken and a maximal stimulating dose of secretin administered intravenously. The duodenal contents are then aspirated and the volume and concentrations of bicarbonate, trypsin and lipase measured.

Bentiromide test

Bentiromide, a substance containing a peptide bond sequence hydrolysed by chymotrypsin, is administered orally. As a reaction to the hydrolysis, PABA is released, absorbed and excreted into the urine where it is easily measured.

Liver Disorders

Serum bilirubin

Serum bilirubin is measured by a diazo reaction whereby *conjugated* (direct reacting) and total bilirubin levels are determined. The *unconjugated* (indirect) bilirubin can then be calculated by simple subtraction. Normal serum bilirubin levels are upto 1.5 mg/100 ml and essentially all of it is unconjugated. Unconjugated hyperbilirubinemia indicates extrahepatic overproduction (hemolysis) or a genetic defect in hepatic uptake or conjugation (*Gilbert syndrome*) of bilirubin.

Conjugated hyperbilirubinemia most often indicates hepatic or biliary tract disease. When it is an isolated abnormality it may also indicate defects of hepatic excretion or storage (*Dubin-Johnson* or *Rotor syndrome)* respectively.

Urine bilirubin or urobilinogen

Bilirubinuria indicates conjugated hyperbilirubinemia and hence hepatic or biliary disease. Urine urobilinogen in excess indicates hepatocellular dysfunction.

Serum alkaline phosphatase

Serum levels of this enzyme reflect contributions from the liver, bones and intestines. Increased hepatic alkaline phosphatase reflects increased hepatic synthesis and increased release due to solubilisation of bits of hepatocyte membrane as a result of the increased tissue levels of bile acids. This is seen in association with cholestasis and neoplastic or granulomatous hepatic disease. *5' nucleotidase* and *γ glutamyl transpeptidase* (GGTP) are also located in the hepatocyte plasma membrane and are similarly released into the circulation. Elevated levels of the latter two enzymes confirm that a high serum alkaline phosphatase signifies hepatobiliary disease.

Transaminases

Aspartate (AST, SGOT) and alanine (ALT, SGPT) aminotransferases are present in large quantities in liver cells and these enzymes are released into the circulation following injury or the death of hepatocytes. Both enzymes are elevated more than three times the normal value in viral, toxic or drug-induced hepatitis. Chronic severe right-sided congestive cardiac failure is also occasionally associated with very high serum levels of these enzymes. Cirrhosis and metastatic liver disease usually produce only modest elevations of these enzymes. An increased ratio of AST:ALT is common in alcoholic liver diseases, especially in alcoholic hepatitis.

Needle biopsy

Biopsy and histologic examination of liver tissue are of value in chronic hepatitis, infiltrative liver disease (hemochromatosis, granulomatous hepatitis) and in metastatic disease. Hemorrhage with hemoperitoneum, biliary leak and hypotension are uncommon complications (<0.5%). The technique is contraindicated in patients with coagulopathies (absolute contraindication) or ascites (relative contraindication).

Peritoneoscopy

This procedure is of diagnostic importance in undiagnosed but suspected liver disease especially for the confirmation of primary or secondary malignancies, cirrhosis and peritoneal tuberculosis. A guided biopsy can be obtained.

Hepatic scintiscan

Technetium-99m sulphur colloid has been used to image hepatic uptake (by Kupffer cells). Filling defects as small as 2 cm can be detected but the test has limited specificity.

ULTRASONOGRAPHY

Abdominal ultrasonography is a non-invasive safe investigation feasible with a portable unit. It is effective in the demonstration of gallstones (ultrasound), virtually replacing oral cholecystography (Fig 13.8) for the diagnosis of cholelithiasis. It is useful for characterising cystic lesions and abscesses in the hepatobiliary and pancreatic system. It is useful in the evaluation of the subject with cholestatic jaundice; dilatation of intra- and extrahepatic biliary system can be detected. Mass lesions of the liver, gallbladder and head of the pancreas are easily detected. It is, however, not as precise for the visualisation of the distal common bile duct and the body and tail of the pancreas, principally due to the overlying gas-filled bowel loops.

Ultrasonography facilitates the drainage of fluid collections and obtaining of specimens by fine needle aspiration for cytologic examination. It is the investigation modality of choice for abdominal disease in pregnancy. Doppler ultrasound is used for assessing patency of the hepatic veins and localising the site of obstruction in portal hypertension.

COMPUTERISED TOMOGRAPHY

With the higher spatial resolution provided by computerised tomography, better images of the hepatobiliary and pancreatic system can be obtained. The CT scan is useful for demonstrating visceral malignancies and delineating the extent of intraabdominal spread. It is the modality of choice for evaluation of complications of pancreatitis such as a pancreatic pseudocyst or an abscess.

MAGNETIC RESONANCE IMAGING (MRI)

MRI of the abdomen is relatively less frequently used for the evaluation of gastrointestinal diseases due to its cost and due to the slow image acquisition resulting in blurred images due to peristalsis. Nonetheless, MRI is

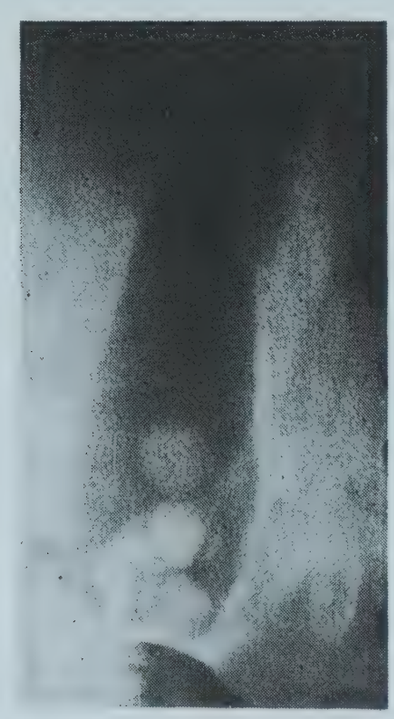


Fig 13.8 Negative stones showing up on an oral cholecystogram

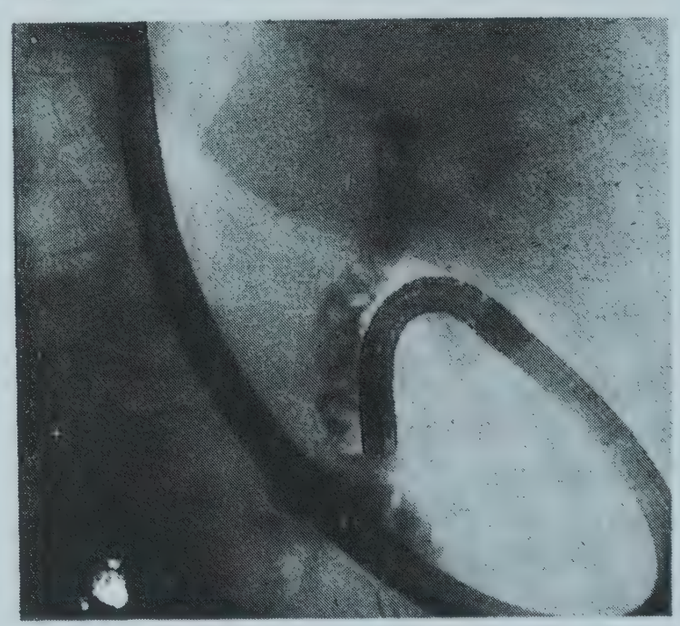


Fig 13.9 ERCP: After the introduction of the duodenoscope, the papilla is sought and cannulated. A water-soluble medium is injected directly into the bile duct. Films are taken during the injection and in this case revealed massive choledocholithiasis

especially useful for evaluating rectal cancers, diagnosing hepatic hemangiomas, differentiating regenerating nodules in a cirrhotic liver from a tumour, and for assessing the resectability of vascular gastrointestinal tumours. MRI also finds specific application in diagnosing hepatic metal overload (iron overload in hemochromatosis, and copper overload in Wilson's disease).

RADIONUCLIDE IMAGING

Scanning with a Technetium-labelled imino diacetic acid derivative (99m Tc HIDA) is useful in the diagnosis of cystic duct obstruction and in acute cholecystitis. Normally within 60 minutes of an intravenous injection, the liver, the gallbladder and the bile ducts can be visualised. In acute cholecystitis the initiating event is most often calculus-induced cystic duct obstruction and this results in visualisation of the common bile duct but non-visualisation of the gallbladder.

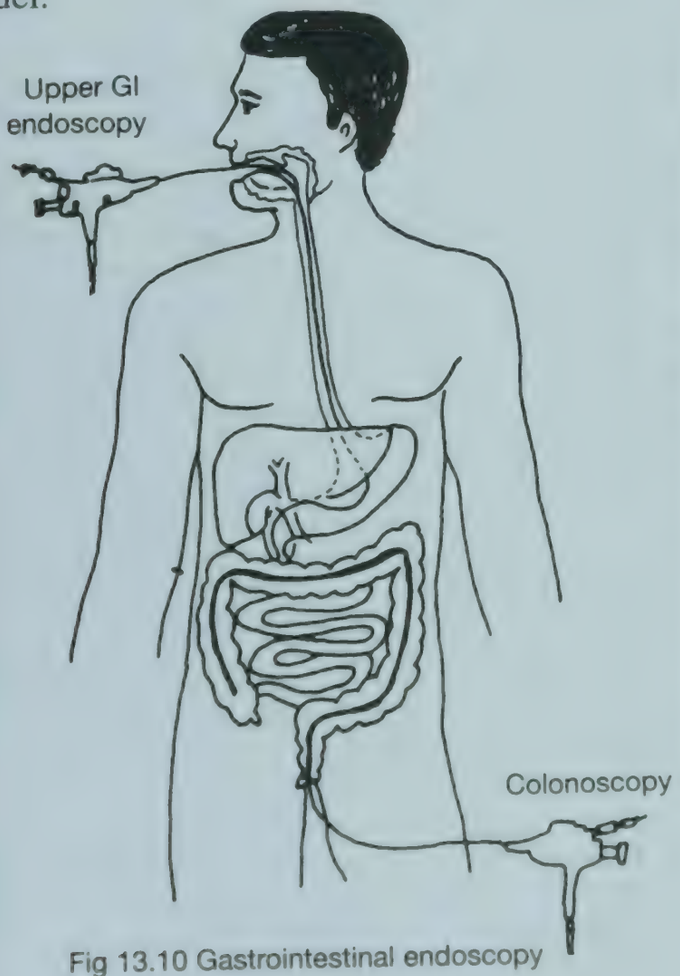


Fig 13.10 Gastrointestinal endoscopy

GASTROINTESTINAL ENDOSCOPY

Esophagogastroduodenoscopy

Upper gastrointestinal endoscopy (Fig 13.10) is performed using a flexible fibreoptic forward-viewing endoscope. The instrument is inserted under direct vision with the patient mildly sedated, topically anesthetised and in the left lateral decubitus position. The entire mucosal surface of the upper gastrointestinal tract can be seen and biopsy or brushings for cytologic examination taken. The endoscope can be used for therapeutic purposes too, for example, for sclerotherapy of varices, thermal electrocoagulation or laser photocoagulation of bleeding lesions and percutaneous endoscopic placement of a gastrostomy.

Endoscopic retrograde cholangiopancreatography (ERCP)

This is performed with a side-viewing endoscope with which the second part

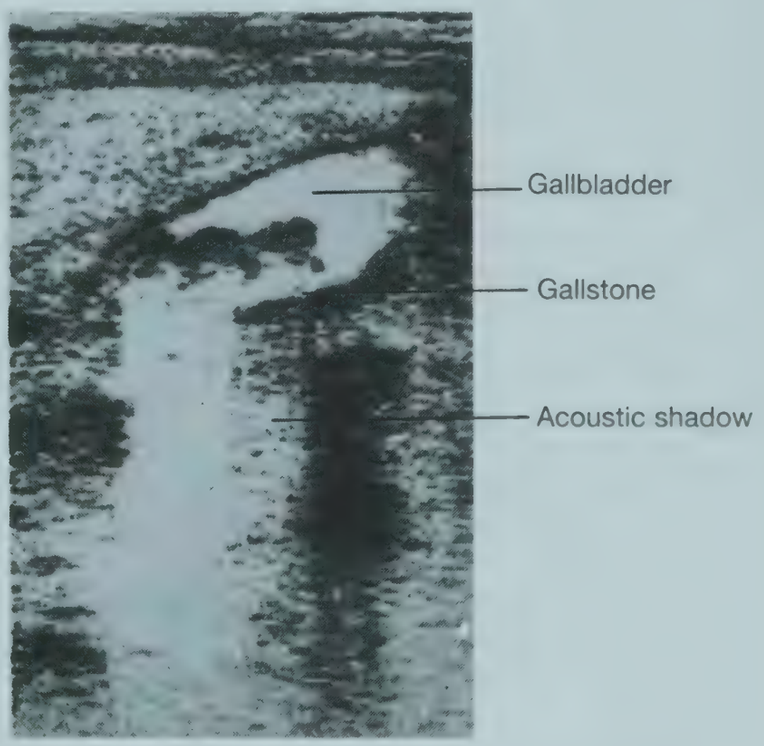


Fig 13.11 Ultrasound showing displaying multiple gallstones of medium size, intense echoes and complete acoustic shadows. Gallstones absorb ultrasound more intensely than soft tissues, thereby producing an 'acoustic shadow' (stone shadow).

of the duodenum is entered and the ampulla of Vater is visualised. The ampulla is cannulated and the cannula adjusted to enter either the bile duct or the pancreatic duct. Radiocontrast material can then be injected to visualise either or both systems. ERCP is performed for diagnostic purposes (as in surgical obstruction), or for therapeutic purposes, for passing a stent, perfusing the bile duct with agents to dissolve calculi, for performing endoscopic sphincterotomy to retrieve a stone impacted at the sphincter.

Colonoscopy and sigmodoscopy

Fibreoptic colonoscopes are similar in design to upper gastrointestinal endoscopes but are longer. After bowel preparation and sedation of the patient, the instrument is inserted to examine the mucosa and to biopsy suspicious areas. Sigmoidoscopes may be flexible or rigid and can reach upto the sigmoid colon. If ischemic or inflammatory bowel disease is suspected, sigmoidoscopy should be done without chemical catharsis to obviate artifacts in biopsy material.

KEY CONCEPTS

Esophageal disorders

- *Esophageal manometry* is used for the evaluation of patients with 'heartburn' or dysphagia. The upper and lower esophageal sphincter tones can be measured with this technique. This technique finds application in the diagnosis of achalasia, diffuse esophageal spasm and for documenting esophageal involvement in systemic sclerosis.
- *Bernstein's acid perfusion test* is a sensitive means of provoking symptoms in patients with chest pain due to reflux esophagitis.
- *Gastric acid studies* consist of measuring BAO and pentagastrin-stimulated MAO. These studies have a role in the diagnosis of the Zollinger-Ellison syndrome and atrophic gastritis.
- *Barium swallow, meal and follow-through* examinations are useful for the diagnosis of mucosal abnormalities (varices), mass lesions, strictures and ulcers (*ulcer crater*) in the esophagus, stomach and upper intestines. The pattern of barium in the small intestines may be informative (flocculation in tropical sprue, deformed ileocecal valve in intestinal tuberculosis).
- *Double-contrast barium enema* studies are useful for evaluating mucosal lesions of the large intestines (Crohn's disease, diverticulosis, ulcerative colitis, cancer).
- *Fecal fat content* is a useful screening test for patients with suspected malabsorption syndrome. It may be qualitative (positive Sudan stain indicates >15 g of fecal fat/day) or quantitative (>6% of ingested fat in a 72-hour stool collection is abnormal).
- The *d-xylose test* is another test of the integrity of mucosal absorptive mechanisms. A 5-hour collection of urine after an oral load of 25 grams of d-xylose must contain 4–5 grams of xylose.
- The *Schilling test* is a test for vitamin B_{12} malabsorption. An abnormal stage 1 (reduced B_{12} absorption) with normalisation in stage 2 (corrected by intrinsic factor replacement) suggests pernicious anemia. When both stages of the Schilling test are abnormal, chronic pancreatitis, bacterial overgrowth or ileal mucosal disease are possibilities.
- *Bile acid breath tests* are helpful in diagnosing syndromes associated with intestinal bacterial overgrowth. The urea breath test is used for the diagnosis of *H. pylori* infection. The hydrogen breath test is used for the diagnosis of lactase deficiency.
- *Small intestinal biopsy* shows diagnostic features in several diseases. The normal villous:crypt ratio is 3:1 or 4:1. Flattened villi are seen in giardiasis, celiac sprue, and intestinal lymphomas. Biopsy permits a specific diagnosis of Whipple's disease (now recognised as due to the bacillus *Tropheryma whipelli*), lymphoma and intestinal lymphangiectasia.
- *Pancreatic function tests* include the *secretin test* (bicarbonate and total fluid output are measured after stimulation with secretin) and the *bentiromide test* (based on release of PABA by chymotrypsin; >60% must be absorbed and excreted in urine).
- *Upper GI endoscopy* is useful in the diagnosis of the etiology of an upper GI bleed (it can demonstrate varices, an ulcer and superficial erosions), for evaluating the patient with dysphagia, and for

obtaining biopsy of suspicious gastric ulcers and gastric masses. Therapeutic indications for endoscopy include sclerotherapy for varices, coagulation of any bleeding source and removal of gastric polyps or foreign bodies.

➢ *Colonoscopy* may be performed for diagnostic purposes such as for evaluating a patient with a lower GI bleed or suspected colonic neoplasm, for assessing the extent of inflammatory bowel disease and for periodic surveillance of patients with familial polyposis. Therapeutic indications include the excision of polyps and reduction of a volvulus or an area of intussusception.

Liver Function Tests (LFT)

➢ LFTs include biochemical tests, serology, imaging studies and liver biopsy.

➢ Bilirubin may be *direct reacting* (conjugated) or *indirect reacting* (unconjugated) and is measured with the *van den Bergh test;* bilirubinuria manifests as high coloured urine and suggests conjugated hyperbilirubinemia. Conjugated bilirubinemia is seen in hepatocellular and biliary disorders, whereas unconjugated bilirubinemia is encountered in hemolytic states and the Gilbert syndrome.

➢ ALP levels are markedly elevated in cholestatic jaundice. The source of ALP can be the liver or the bone. Elevated 5' nucleotidase or γ-GTP levels suggest a hepatic cause of elevated ALP. γ-GTP is also a marker of alcoholic hepatic injury.

➢ AST (SGOT; present in muscle, brain, kidneys), ALT (SGPT; present principally in liver) are elevated more than 3 times the normal levels in hepatitis. AST/ALT >2 suggests alcoholic hepatitis. LDH is a less specific marker of hepatitis (it is present in the heart and the red blood cells.)

➢ Serum albumin is a useful prognostic marker in hepatic cirrhosis with portal hypertension. Plasma ceruloplasmin level is reduced in Wilson's disease. Serum transferrin and ferritin levels are elevated in hemochromatosis.

➢ *US* is the investigation of choice for gallstones, for bile duct evaluation (intra- vs extrahepatic cholestasis), and for investigating abscesses and cysts in the liver. It also corroborates the diagnosis of Budd-Chiari syndrome by demonstrating an enlarged caudate lobe. Doppler US is helpful in localising the site of obstruction in HVOT obstruction.

➢ A *liver scan* is useful for suspected hepatic mass lesions; cholescintigraphy is the investigation of choice for acute cholecystitis.

➢ CT is the investigation of choice for evaluating hepatic mass lesions, for documenting an alcoholic fatty liver, and for demonstrating the parenchymatous iron overload in hemochromatosis.

➢ *ERCP* is ideal for evaluation of the distal biliary tree; *PTC* is preferable for evaluation of the biliary tree above the common hepatic duct.

➢ *Liver biopsy* is useful for evaluating chronic hepatitis (CAH vs CLH vs CPH), a suspected SOL or granulomatous hepatitis.

13.4 Peptic ulcer disease

PEPTIC ULCER DISEASE

A peptic ulcer refers to a breach in the duodenal or gastric mucosa which extends through the muscularis mucosa into the submucosa, or deeper. The term 'peptic' emphasises the role of peptic proteolysis in the pathogenesis. A breach in the mucosa which is more superficial is called an *erosion.*

Epidemiology Peptic ulcer affects men more often than women, though this male predominance is now diminishing. The onset of symptoms is unusual in the prepubertal years or later than the age of 65 years. Among the established risk factors for peptic ulcer disease are a family history of ulcer disease, and the use of tobacco, aspirin or other non-steroidal antiinflammatory drugs (NSAIDs). There is also an association with chronic medical ailments such as cirrhosis, chronic renal insufficiency and chronic pulmonary disease. While the role of personality type and stress have been invoked in the pathogenesis of disease, the use of alcohol or caffeine have not been demonstrated as independent risk factors for peptic ulcer formation. The association of peptic ulcer with *Helicobacter pylori* infection is discussed in detail below.

Pathogenesis Earlier the formation of a peptic ulcer (Fig 13.12) was regarded as essentially the consequence of acid hypersecretion with acid-induced mucosal injury.[1] In recent years more attention has been focused on defence mechanisms of the gastroduodenal mucosa rather than on acid pepsin factors. Available evidence suggests that only 50 per cent of patients with duodenal ulcers secrete excess amounts of acid. Further, only some acid needs to be present for ulcer development and in some cases benign ulcers may develop in the absence of gastric acid.

It is now recognised that synthesis of mucosal prostaglandins maintains an effective gastroduodenal mucosal barrier. Deficient production of mucous and a modified mucosal barrier not only increase the risk of ulcer development but can lead to ulceration without acid hypersecretion. Impaired prostaglandin formation occurs with tobacco use, with the use of NSAIDs and with *Helicobacter pylori* infection.

The role of *Helicobacter pylori* infection in the pathogenesis of peptic ulcer is becoming clearer. The organism is clearly the cause of antral gastritis. It is found in almost 100 per cent of periulcer gastric epithelium (as against a prevalence rate of 20 per cent in the gastric mucosa of normal subjects). Antibiotic therapy directed against the organism heals ulcers, and failure to eradicate infection is associated with delayed and incomplete healing, ulcer recurrence and relapse.

[1] Acid hypersecretion could be due to an increased parietal cell mass and the increased sensitivity of parietal cells to gastrin, or due to a lesser acid-induced inhibition of gastrin release.

Hypergastrinemia due to a non ß-pancreatic
let-cell neoplasm (Zollinger-Ellison syndrome)
associated with multiple peptic ulcers which
re refractory to conventional therapy.

athophysiology and clinical features The
linical features of a peptic ulcer depend on its
ze, its location and the extent of inflammation,
long with 'host-dependent factors' such as, the
ge of the host, and the presence or absence of
iabetic neuropathy. The larger the ulcer, the
loser the location near the pylorus, the greater
ne inflammation, and the younger the subject,
ne more classic is the presentation. Such a
lassic presentation may be seen in less than
0 per cent of subjects.

A burning epigastric pain that occurs typically
–3 hours after meals, is rhythmic in its relation
o food ingestion, and is periodic in its pattern of
ecurrence, is the classic clinical hallmark of a duodenal ulcer. There may be a history of nocturnal or early morning awakening, and of relief of pain with intake of food/milk. The postprandial character of pain is related to the reduced buffering of gastric acid with emptying of digested gastric contents. The pain of peptic ulcer is chronic, with resolution occurring either spontaneously or in response to therapy. This pattern of pain is suggestive of either a duodenal or a gastric ulcer; clinical differentiation between the two is difficult.

Atypical presentations with vague abdominal pain and without a consistent relationship to meals is common in the elderly, in diabetics and in subjects with a defective perception of pain.

Complications of peptic ulcer disease include gastric outlet obstruction, penetration (anteriorly or posteriorly into adjacent viscera), perforation with consequent peritonitis, and upper gastrointestinal bleeding.

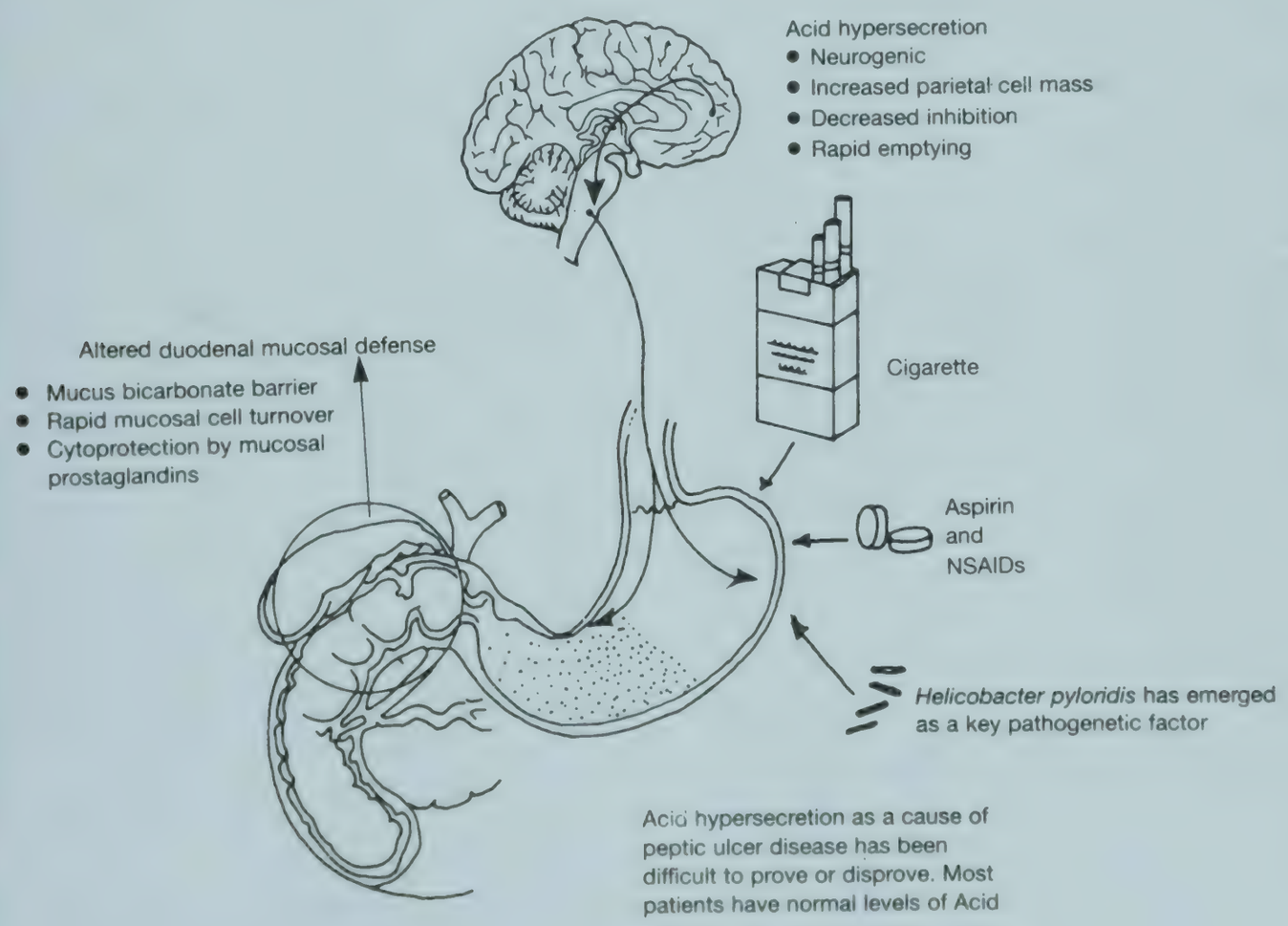


Fig 13.12 Etiopathogenesis of a peptic ulcer

Physical findings are unremarkable in the absence of complications. Auscultatory evidence of a succession splash more than three hours after a meal suggests gastric outlet obstruction. The presence of a history of early satiety and recurrent 'retention-type' vomiting strengthens clinical suspicion of this entity. A high ulcer (in the cardia) can present as transport dysphagia. Anterior penetration can mimic biliary disease while posterior penetration can simulate pancreatitis.

Diagnostic approach A classical history in a subject less than 50 years old justifies empirical therapy. Onset beyond the fifth decade, atypical symptoms, persistence or prompt recurrence after empirical therapy indicate the need for further evaluation.

The choice of the initial diagnostic procedure is between a double contrast barium meal (DCBM) and esophagogastroduodenoscopy. The typical radiologic appearance is the presence of a discrete ulcer crater in the proximal duodenal bulb. A DCBM is economical, less hazardous and has widespread feasibility in a community. It has however, a sensitivity of 80–90 per cent and does not yield tissue for histopathology or fluid for microbiologic evaluation (for *Helicobacter pylori*). An endoscopy has a higher sensitivity (near 100 per cent) with additional facility for biopsy and detecting Helicobacter species. It is, however, expensive and not without risk in the elderly and in the presence of cardiopulmonary disease. Gastric ulcers more than 2 cm in size, located on the greater curvature or with radiologic effect of a mass lesion must be subjected to multiple biopsies choosing six sites around the ulcer edge to rule out malignant lesions. Follow-up endoscopy of benign lesions is recommended after eight weeks to confirm complete healing. Because of its content of the enzyme urease, a diagnosis of *Helicobacter pylori* infection is feasible with a breath urea test or with the culture of antral biopsy in urea containing broth.

An unusually resistant ulcer, the presence of multiple or ectopic ulcers, a family history of ulcer disease, a concomitant history of recurrent diarrhea or hypercalcemia may indicate the need for a work-up of the patient to exclude the diagnosis of Zollinger-Ellison syndrome. Three separate fasting gastrin levels should be obtained. A serum gastrin level exceeding 1000 pg/ml is virtually diagnostic of Zollinger-Ellison syndrome. If the values are in the range 500–1000 pg/ml, a *secretin provocation test* may be used. Whereas in normal subjects an intravenous injection of secretin suppresses serum gastrin levels, subjects with Zollinger-Ellison syndrome demonstrate a paradoxical rise in serum gastrin levels (usually more than 200 pg/ml above the basal values) within five minutes of administration of secretin.

Management

Medical treatment: Drug treatment of peptic ulcer disease involves attempts at acid suppression, acid neutralisation and enhancing mucosal resistance (called *cytoprotection*). Acid suppression is possible by blockade of H_2 receptors or M_1 receptors on the parietal cells, or by inactivation of the enzyme H^+–K^+ATPase that drives the proton pump of the parietal cells. H_2 receptor blockade is widely used with one of the several commercially available agents: cimetidine (400 mg bid), ranitidine (300 mg hs or 150 mg bid), famotidine (40 mg h.s or 20 mg bid); or nizatidine (300 mg h.s. or 150 mg bid). The overall efficacy of a six-week course is 80–90 per cent. Apart from an initial treatment failure of 10–20 per cent, recurrence after medical treatment may occur in 25 per cent of subjects. Recurrences within three months of healing, or multiple recurrences (more than two within a year) indicate the need for maintenance therapy.

The proton pump blocker omeprazole (20–40 mg single daily dose) is very effective but expensive and hence is used mainly in subjects with the Zollinger-Ellison syndrome. Anti-muscarinic agents like the M_1 receptor blocker pirenzipine are also effective but therapy is associated with side effects.

There is also sufficient data to indicate that acid neutralisation with antacids (taken at one and three hours postprandially and at bedtime for 4 weeks) is an effective option to H_2 blockers.

Cytoprotective agents include agents that enhance the production of gastric mucous, prostaglandins and bicarbonate, and also increase binding of bile salts and pepsin. Sucralfate is one such agent (effective in doses of 1 g qid or 2 g bid for 6–8 weeks). Colloidal bismuth compounds are the other agents that are specifically preferred when the organism *Helicobacter pylori* is isolated. A triple regimen comprising of bismuth (subsalicylate 2 tablets of 262 mg qid or tripotassium dicitrate 120 mg qid), metronidazole (0.6-1.5 g per day) and tetracycline (500 mg qid) for 2 weeks is effective against H. pylori. Amoxicillin (1.5-2 g per day) may be used in place of tetracycline. Synthetic prostaglandins (misoprostol) are principally used for the prophylaxis of ulcers induced by NSAIDs in subjects consuming the latter.

Cessation of smoking and avoiding abuse of NSAIDs are important adjuncts to therapy. Bland diets which are free of spices are of no proven benefit.

Surgical treatment: Surgery for peptic ulcer is indicated whenever the medical management has failed or when acute or chronic complications supervene. The surgical procedures involve attempts to decrease acid secretion by reducing the cephalic phase of gastric secretion *(vagotomy)* or the gastric phase of gastric secretion (*antrectomy* to remove the major source of gastrin). Various drainage procedures are performed concomitantly to maintain gastric emptying. Proximal vagotomy (also called *superselective*) is being used increasingly instead of truncal vagotomy so that acid secretion can be reduced without any adverse effect on gastric emptying.

NON-ULCER DYSPEPSIA

The term *non-ulcer dyspepsia* is used when the clinical history suggests a peptic ulcer but investigations (endoscopy or barium X-ray) fail to reveal one. The pathogenesis of this disorder is unclear although it is twice as common as peptic ulcer disease. Non-ulcer dyspepsia does not respond consistently to standard peptic ulcer therapy.

KEY CONCEPTS

Peptic ulcer

- Ulcers (unlike erosions) extend through the muscularis mucosa. The development of an ulcer reflects an imbalance between damaging factors (*acid* and *pepsin*), and mucosal protective factors (*mucus, blood flow, membrane barriers*). Hypersecretion is more important in the pathogenesis of duodenal ulcer (DU), whereas decreased mucosal resistance plays a prominent role in gastric ulcers (GU).
- The major etiologic factors include *H. pylori* infection, smoking, alcohol and NSAIDs.There is an association with COAD, renal failure and hepatic cirrhosis.
- Burning epigastric pain relieved by food and recurring 2–3 hours later is pathognomonic of a peptic ulcer. Nocturnal awakening with pain is also quite suggestive. Symptoms cannot reliably distinguish DU from GU, although in GU patients food may increase abdominal pain. Complications of a peptic ulcer include *bleeding, perforation, penetration* and *outlet obstruction*. A GU (but not a DU) can undergo malignant transformation.
- The diagnostic modality of choice is endoscopy; it is replacing double-contrast barium examination. A urea breath test may be performed to substantiate H. pylori infection. Serum gastrin levels may be obtained if Z-E syndrome suspected. A suspicion of Z-E syndrome is entertained in the following situations: multiple ulcers, recurrences, ulcers that are refractory to medical treatment, a family history of MEN I, or postbulbar location of a duodenal ulcer.
- Management includes restriction of alcohol, coffee and cessation of smoking. The role of diet is little beyond avoiding known provocative foods. Triple therapy (metronidazole, bismuth, tetracycline) for eradication of H. pylori is recommended for all ulcer patients. Non-absorbable antacids, administered 1 hour and 3 hours after food, decrease symptoms, promote healing, reduce recurrences. H2-receptor antagonists (at bedtime) are currently the treatment agents of choice in view of patient convenience, a sustained reduction of acid output and increased ulcer healing with fewer relapses; a maintenance dose (at $^1/_2$ dose) is recommended to avoid recurrence. Mucosal cytoprotective agents (1 hour prior to meals) too are effective alternatives. Proton pump inhibitors and anticholinergics are useful adjuncts for managing refractory cases. Misoprostol has been used for prophylaxis of NSAID-associated ulcers. Surgery is reserved for severe, refractory disabling symptoms and for complications; options include antrectomy or partial gastrectomy for GU, and selective vagotomy for DU.

13.5 Malabsorption syndromes

Classification For the purpose of simplicity, malabsorption syndromes may be classified into three categories. First, there may be *defective intraluminal digestion* of nutrients owing to impaired delivery of digestive enzymes or bile salts that are needed for lipid processing. Second, there may be a *defective uptake* of nutrients due to damage to or scarcity of the absorptive epithelium. Third, there may be *defective transport* of absorbed nutrients from the mucosa to the systemic circulation due to lymphatic disease (Table 13.11). Such a classification is simplistic as in several conditions more than one pathophysiologic process may participate.

Clinical features Whatever be the underlying etiology, the clinical features of the malabsorption syndrome are similar. In the early stages of the disease the stools are observed to be bulky, sticky and tend to float (because of increased gaseous content). Weight loss, malaise and other signs of hypoproteinemia and hypovitaminosis soon develop. Thus, there may be chronic diarrhea, glossitis, stomatitis, follicular hyperkeratosis and dermatitis. There may be a nutritional anemia, and bone pain related to osteopenic bone disease is not infrequent. The endocrine system may be secondarily involved with symptoms such as amenorrhea and infertility. In certain deficiency states (such as vitamin B_{12}, thiamine), a peripheral neuropathy may be prominent.

Clinical diagnostic approach The approach to a patient with malabsorption syndrome is outlined in Fig 13.13.

Table 13.11 Classification of malabsorption syndrome

A. Inadequate digestion*
1. Pancreatic exocrine deficiency
2. Intraluminal bile salt deficiency
3. Disaccharidase deficiency

B. Inadequate absorption*
1. Mucosal damage
   - tropical sprue
   - giardiasis and other intestinal parasitoses
   - Infiltrative disorders
     - immunoproliferative small intestinal disease (IPSID)
     - amyloidosis
     - lymphoma
   - fibrosis
   - systemic sclerosis
2. Inadequate absorptive surface
   - inflammatory bowel disease (tuberculosis, Crohn's disease)
   - short bowel syndrome

C. Lymphatic obstruction*
1. Lymphoma
2. Whipple's disease
3. Lymphangiectasia

* Frequently, more than one mechanism may be operative in a given disease.

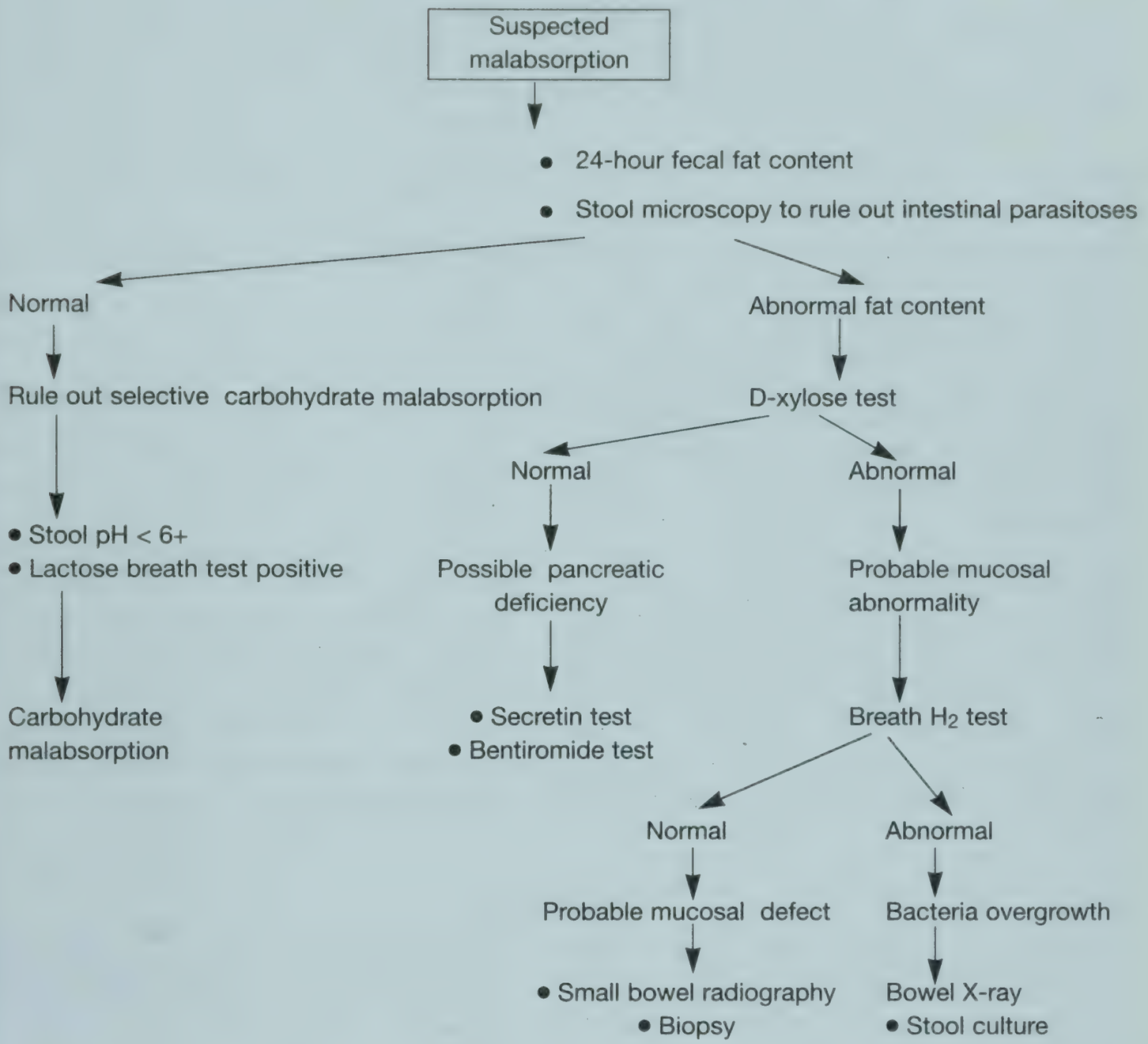


Fig 13.13 Approach to a patient with a malabsorption syndrome; the individual tests are discussed in section 13.3.

Specific Causes

Tropical sprue

Tropical sprue is a chronic disorder acquired in endemic tropical areas which is characterised by abnormalities of small bowel structure and function which become progressively more severe unless treated.

Distribution Tropical sprue is common in the Indian subcontinent, southeast Asia, southern parts of Africa, northern part of South America and the West Indies.

Etiopathogenesis There is some suggestion that tropical sprue may be related to persistent chronic intestinal contamination with one or more enteric pathogens, especially the coliforms. However, jejunal aspirates of diseased persons in south India have not yielded coli forms consistently.

Natural history The natural history is variable but usually the disorder is progressive with development of multiple nutritional deficiencies within six months.

Pathology In the early stages of the disease the abnormalities are more in the jejunum but the ileum too is involved soon. The villi are thickened to form 'leaves' (rather than the normal finger-like appearance) and occasionally are fused to form ridges. Microscopically, the villi are short and broad, the crypt area lengthens, the epithelium becomes cuboidal/pseudostratified (normally it is columnar) and there is an inflammatory infiltrate of mononuclear cells.

Treatment A high calorie, high protein, low fat diet is instituted. Folic acid, 10–20 mg daily, is given for a few weeks and it corrects the diarrhea, anemia and glossitis without much improvement of the intestinal lesion. Tetracycline, 250 mg four times daily, helps eradicate coliforms and improves the intestinal lesion. The treatment may be given for 4–6 weeks. If the patient has vitamin B_{12} deficiency or when serum levels cannot be obtained, treatment should include parenteral injections of 1000 mg vitamin B_{12} for several days, followed by monthly injections.

Immunoproliferative small intestinal disease (IPSID)

Previously called the Mediterranean abdominal lymphoma, this disorder is endemic in West Asia. It occurs in males who are under 30 years of age and who are of a low socioeconomic status. It has a high incidence of heavy chain paraproteinemia and typically involves the duodenum and proximal jejunum. Clubbing, steatorrhea and chronic abdominal pain are the usual clinical features. Edema, nutritional anemia and ascites may be present. Small intestinal biopsy and the finding of the paraprotein on serum electrophoresis are diagnostic. Radiotherapy and chemotherapy have both been used for treatment.

KEY CONCEPTS

- Malabsorption syndrome is characterised clinically by bulky, pale, frothy, greasy stools. Associated clinical features include weight loss, multiple nutritional deficiencies, anemia, dermatoses and bleeding tendencies.
- Malabsorption may be due to *maldigestion* (chronic pancreatitis, biliary obstruction), due to *mucosal defects* (sprue, inflammatory bowel disease, Whipple's disease, abetalipoproteinemia), or may result from *lymphatic obstruction* (intestinal lymphangiectasia, lymphoma).
- Fecal fat content is a good screening test for fat malabsorption. The *^{14}C triolein breath test* also identifies fat malabsorption.
- A lowered stool pH may occur in carbohydrate malabsorption; the *hydrogen breath test* can identify disaccharidase deficiency.
- ^{51}Cr-labelled albumin identifies a protein losing enteropathy. The *^{14}C-glycocholate breath test* identifies bacterial overgrowth syndromes and terminal ileal disease. The *Schilling test* assesses vitamin B_{12} absorption. The *bentiromide* and *secretin* tests identify pancreatic exocrine dysfunction. The *d-xylose* test identifies mucosal integrity as it does not require digestion.
- Small intestinal biopsy may be helpful if it reveals *total villous atrophy* (e.g. sprue), *subtotal villous atrophy* (bacterial overgrowth, ischemia, partially-treated celiac disease) or *non-villous abnormalities* (PAS-positive macrophages in Whipple's disease; giardiasis, lymphoma, lymphangiectasia). Biopsy may be processed to evaluate the activity of *brush border enzymes*.
- *Topical sprue* is an important cause of malabsorption syndrome in India; it may be due to a combination of nutritional and infectious factors.
  - there is evidence of villous atrophy, crypt hyperplasia, and infiltration of the lamina propria by lymphocytes and plasma cells.
  - a 4-week course of tetracycline and supplementation with vitamin B_{12} and folic acid is recommended.

13.6 Inflammatory bowel disease

Inflammatory bowel disease refers to disorders of unknown etiology characterised by chronic inflammation of the intestines (large or small bowel or both). Usually ulcerative colitis and Crohn's disease are the two disease entities included in this category. However, we shall also discuss intestinal tuberculosis in this chapter, since the clinician frequently has to differentiate between these disorders.

Ulcerative Colitis

Ulcerative colitis is a chronic inflammatory disorder of unknown etiology, affecting the mucosa of the colon and manifesting as diarrhea and/or rectal bleeding.

Epidemiology The disease affects both sexes equally with a peak age of incidence ranging from 15 to 30 years. Western data indicates that, as compared to African Americans the disorder is four times more common in caucasians especially in Jews. The disease in more common in the urban areas.

Etiopathogenesis Infectious, autoimmune and psychosomatic mechanisms have been put forth to account for the disease. No mechanism in isolation can satisfactorily explain the clinical syndrome of ulcerative colitis. Probably, a defect in mucosal immunity triggers off an enhanced immune response to a luminal antigen in a susceptible individual. This immunoinflammation leads to the local and systemic features of the disease.

Pathology and physiology The disease affects only the left-sided colon (descending colon) in three-fourths — this is known as *colitis;* in the rest the entire colon is affected — this is known as *pancolitis.* The hallmark of the disease is continuous inflammation of the mucosa and submucosa of the colon without any intervening normal areas. The epithelium of the crypts of Lieberkuhn is necrotic and studded with micro-abscesses referred to as *crypt abscesses.* The inflammatory cell infiltrate consists of polymorphonuclear leukocytes and lymphocytes. The destroyed epithelium attempts to regenerate. The distorted architecture of some of the regenerating crypts results in mucosal excrescences referred to as *pseudopolyps.* In longstanding cases, the inflammation extends below the submucosa and the muscularis mucosae undergo hyperplasia and fibrosis. The result is a short fibrotic colon that has lost its haustrae and has strictures at areas of extreme fibrosis.

The mucosa is friable and bleeds easily accounting for blood in the stools. The denudation of the mucosa results in loss of colonic water absorption capacity with consequent diarrhea. Intense inflammation extends to the muscular layer of the colonic wall. Colonic muscular tone is impaired with resultant dilatation of the colon, which in its extreme form is referred to as *toxic megacolon.* Barium enemas, opiates and anticholinergic drugs (both drugs decrease colonic motility) seem to be precipitating factors. Extension of inflammation

Natural history The natural history is variable but usually the disorder is progressive with development of multiple nutritional deficiencies within six months.

Pathology In the early stages of the disease the abnormalities are more in the jejunum but the ileum too is involved soon. The villi are thickened to form 'leaves' (rather than the normal finger-like appearance) and occasionally are fused to form ridges. Microscopically, the villi are short and broad, the crypt area lengthens, the epithelium becomes cuboidal/pseudostratified (normally it is columnar) and there is an inflammatory infiltrate of mononuclear cells.

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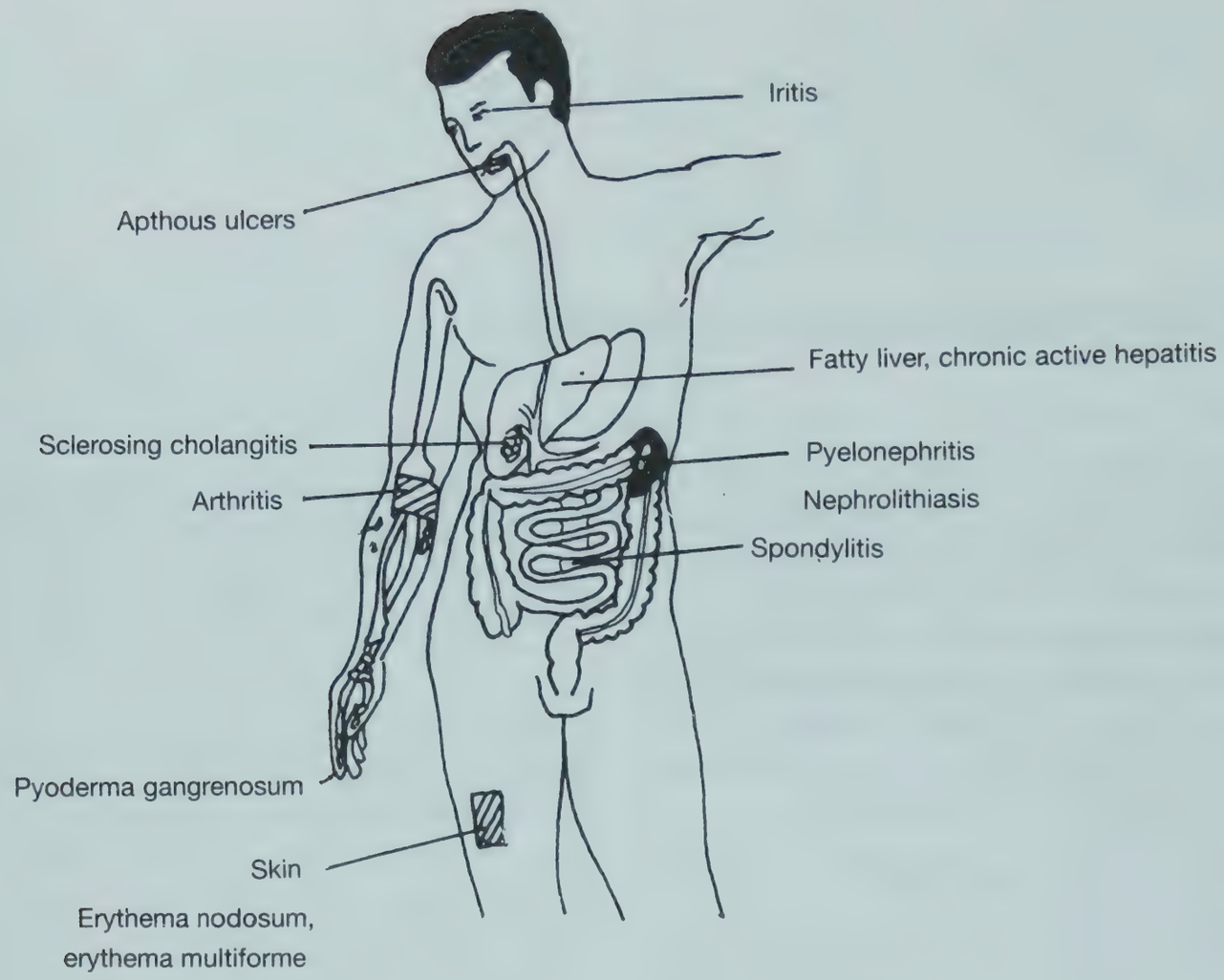


Fig 13.14 Extraintestinal manifestations of ulcerative colitis

to the serosa, which is very rare, can result in colonic perforation as well. After several years of inflammation, the epithelium can become dysplastic and finally transform into a frank carcinoma which, understandably, tends to be multicentric.

Clinical features The location and extent of colonic inflammation seem to predict the clinical features of the disease. More than half the patients have *mild* ulcerative colitis with the pathology either confined to the rectum (when the condition is called *ulcerative proctitis*) or the left-sided colon (*left-sided colitis*). The main symptom is rectal bleeding with or without diarrhea, and virtually no systemic features. Isolated rectal involvement can manifest as only tenesmus and constipation. About a third of patients have *moderate* ulcerative colitis which is characterised by significant diarrhea (4–6 loose bloody bowel movements per day). Abdominal cramps and low grade fever may be present. Roughly 15 per cent of patients have extensive colonic involvement with intense inflammation which is called *severe* or *fulminant* ulcerative colitis. These patients are weak, pale and prostrated due to severe bloody diarrhea (more than ten loose, bloody bowel movements per day) and the consequent anemia, hypovolemia and hypotension. They are febrile and abdominal examination reveals a generalised tenderness. Two physical signs to be actively sought in such a sick patient are the presence of bowel sounds and presence of rebound tenderness. An absence of bowel sounds probably signifies the complication of toxic megacolon and the presence of rebound tenderness suggests the possibility of perforation

with peritoneal inflammation. Severe ulcerative colitis is usually associated with the laboratory findings of leukocytosis and an elevated erythrocyte sedimentation rate.

Patients with ulcerative colitis may also manifest with changes in extraintestinal organs and tissues (Fig 13.14). Of these, arthritis (20%), iritis (10%) and skin involvement (10%) are encountered frequently. Arthritis is most often a peripheral arthritis, follows the bowel symptoms and waxes and wanes with intestinal symptoms. HLA B-27 positive individuals tend to develop sacroiliitis and spondylitis, the course of which is dissociated from the intestinal symptoms. Mild abnormalities of liver function are also frequent and correlate with fatty infiltration of the liver or non-specific hepatitis. Rarer but more serious complications include pericholangitis (inflammation around bile ductules in the portal tract), sclerosing cholangitis (dense fibrosis added to the previous entity) and cholangiocarcinoma. Skin manifestations include erythema nodosum and pyoderma gangrenosum. The latter condition is characterised by extensive ulceration of the extremities and occurs during bouts of colitis.

Diagnostic methods A definitive diagnosis of ulcerative colitis is made by the sigmoidoscopic appearance of a diffusely reddened, ulcerated friable mucosa, provided specific infections (amebiasis, shigellosis, campylobacter colitis) have been excluded by appropriate stool cultures and microscopic examinations. The diagnosis may be supported by radiologic examination. Colonoscopy plays no role in the diagnosis of acute ulcerative colitis; in fact, in the acute stage it may well be contraindicated because of the risk of perforation. It is, however, invaluable in the follow-up of a chronically diseased colon for detecting dysplastic lesions or microinvasive cancer.

A double contrast (barium and air) barium enema may also be used in the chronic stage of the disease to clinch the diagnosis in cases where sigmoidoscopy is equivocal, to outline the severity and extent of the disease where the diagnosis is already made, and to detect complications such as strictures or superimposed malignancy. The mucosa on barium enema shows a diffuse granular appearance reflecting extensive ulceration, with filling defects indicating pseudopolyps. Mucosal edema appears as a *thumbprinting* pattern. The colon loses its normal haustral pattern (lead-pipe colon) and the presacral space is increased reflecting a pulled-up, fibrotic rectum. Plain X-ray of the abdomen is indispensable in the diagnosis of complications; a diameter of the transverse colon more than 6 cm suggests a toxic megacolon, and gas under the diaphragm suggests a perforation.

Natural history In the majority of patients the disease follows a waxing and waning course with intermittent bouts of colitis interspersed with periods of remission of a variable duration. A small percentage (10 per cent) have persistent symptoms and a minority have lasting remission after an initial episode. Colonic strictures (seen in five per cent) may modify the clinical course. Superimposed cancer occurs as a complication which increases in incidence with the extent of disease and its duration. The risk is about one per cent per year in the initial two decades, rising steeply thereafter.

Treatment The basic aim of therapy is to control the acute stage of the disease, prevent recurrences and to detect complications at the earliest stage. The traditional pharmacologic therapy has revolved around sulfasalazine and corticosteroids used topically or by systemic administration. However, with the overwhelming evidence indicating immunoinflammation as the mechanism of mucosal damage, immunomodulators (such as cyclosporin A, levamisole, methotrexate) and inhibitors of inflammatory mediator release and production (lipoxygenase inhibitors like zileuton, eicosapentaenoic acid) are now emerging as possible therapeutic modalities.

General measures include permitting the patients to eat whatever they can tolerate and using antidiarrheal medications very sparingly (since these are known to precipitate toxic megacolon). Mild ulcerative colitis presenting mainly as proctitis can be treated either with sulfasalazine given orally (2–4 g/day in four divided doses) or as an enema. Steroid enemata can also be used.

Moderate ulcerative colitis can also be treated on an outpatient basis with oral prednisolone (40–60 mg/day) along with sulfasalazine initially, followed by maintenance with oral sulfasalazine alone.

Severe ulcerative colitis necessitates hospitalisation, administration of intravenous fluids and intravenous steroids (continuous infusion of hydrocortisone, 300 mg/day), followed by oral sulfasalazine and steroids. Lack of response to this intensive regimen may indicate the need for surgical intervention.

Toxic megacolon is managed with bowel rest, nasogastric suction and parenteral steroids. If there is no improvement within 48–72 hours or if there is evidence of perforation, surgery must be undertaken promptly.

The surgical procedures employed are several: proctocolectomy with a continent ileostomy (Koch pouch), proctocolectomy with ileoanal anastomosis, and colectomy with rectal mucosectomy with ileorectal anastomosis. The latter procedure maintains sphincter control.

The use of cyclosporin A, levamisole and methotrexate should be limited to investigative studies only till definitive benefits are proven. Newer modifications of 5′ aminosalicylic acid include sustained release preparations and 'diazo bond' containing preparations (olsalazine, balsalzide); the latter are supposedly less toxic as the sulfapyrine moiety of sulfasalazine is replaced by an inert one. Rapidly metabolised topical steroids (budesonide, toxiocortol) are also being tried, in an effort to reduce systemic absorption. Sodium cromoglycate and sucralfate are two other drugs that have shown promise in the treatment of distal colitis, when used as retention enemata.

The risk of cancer is best countered with yearly colonoscopies and colonoscopy-guided multiple mucosal biopsies of suspicious areas (once the duration of colitis exceeds seven years in a patient with pancolitis and 15 years in a patient with left-sided colitis alone). Severe degrees of dysplasia are treated with colectomy while mild degrees are followed up carefully increasing the frequency of colonoscopy to once every three months.

Crohn's Disease

This is a disorder of unknown etiology characterised by chronic granulomatous inflammation of the ileum and the colon.

Epidemiology Like ulcerative colitis, this disease is more common in young Caucasians, especially Jews. It is rare in India.

Etiopathogenesis Psychogenic, autoimmune and infectious mechanisms have been propounded, but none can satisfactorily explain the pathogenesis of the disorder. A few recent reports had highlighted the isolation of *Mycobacterium tuberculosis* from the intestines of affected patients; still others have negated the above finding by failure to demonstrate the organism using such sophisticated techniques as the polymerase chain reaction.

Pathology Pathologically, Crohn's disease is a discontinuous transmural granulomatous disease that affects the ileum (hence called 'ileitis' or regional 'enteritis') and the adjacent right colon (ascending colon). Being a transmural inflammation, there is a tendency for stricture formation, fistula formation, and for loops of bowel to adhere, resulting in abdominal masses. The mucosa has a nodular appearance *(cobble stoning)* and *skip areas* of normal mucosa interspersed between the abnormal areas.

Clinical features The typical patient is a young person with a history of episodic postprandial abdominal pain (often periumbilical), low grade fever and mild diarrhea. The patient has, on abdominal examination, right lower quadrant tenderness or occasionally a palpable mass. Diarrhea is generally less severe than in ulcerative colitis; stools are not grossly bloody. Diarrhea is related to mucosal damage. Abdominal cramps and colic probably represent varying degrees of intestinal obstruction. Constant dull abdominal pain raises the possibility of an inflammatory mass or abscess, whereas constant severe pain may signify a perforation of the diseased intestines.

Extraintestinal manifestations are more common than in ulcerative colitis and include arthritis, uveitis, skin lesions, hepatic lesions and cholelithiasis.[1]

Diagnosis No laboratory test is diagnostic of the disease. Contrast barium studies of small bowel may reveal loss of normal mucosal pattern and segmental narrowing.

Treatment Treatment is aimed at improving symptoms since there is no cure for the disease. General measures include providing adequate nutrition, trial of oral sulfasalazine for colonic disease (it is ineffective in pure ileitis) and the use of metronidazole in the presence of perianal disease. Metronidazole (10 mg/kg/day) may also be useful in acute exacerbations of the disease as are steroids. Hydroxychloroquin (Plaquenil) has shown promise in recent reports.

Intestinal Tuberculosis

Epidemiology In the era before effective chemotherapy for tuberculosis was evolved, intestinal tuberculosis was most often secondary to the swallowing of infected sputum in patients with cavitary lung disease. Today, the commonest form of the disease is a primary form, due to direct intestinal mucosal penetration. The disease is more common in young adults (with women being affected more than men in some Indian series). The disease seems to be more common in the poorer socioeconomic sections of society.

Pathogenesis and pathology The ingested *Mycobacterium tuberculosis* bacilli lodge in the ileocecal region (55–75 per cent of cases) or in other adjacent areas of the jejunum and colon. The abundance of lymphoid tissue and increased stasis of food contents in the ileocecal region may account for this localisation. The bacilli infiltrate into the submucosal lymphoid tissue and produce the characteristic granulomatous inflammation. Caseation necrosis may or may not be present and tends to be more common in the mesenteric lymph nodes invaded by the bacilli. The lymphangitis results in superficial circumferential ulcers that tend to have their long axis perpendicular to the lumen (the lymphatics tend to encircle the intestinal wall).

Morphologically, three forms of the disease are seen. The *ulcerative type* of lesion (60 per cent) is probably related to infection with a high load of virulent bacilli; diarrhea related to mucosal damage results. The *hypertrophic type* (10 per cent) is characterised pathologically by scarring, fibrosis and heaped-up mass lesions; it may be related to infection with a lesser number of bacilli of attenuated virulence. Symptoms of intestinal obstruction are the dominant complaints. *Ulcero-hypertrophic forms* (30 per cent) are characterised by the occurrence of both patterns of disease.

The ileocecal valve is frequently damaged and rendered incompetent (as distinguished from Crohn's disease), and the mesenteric lymph nodes are also involved.

Clinical features There are no specific symptoms or signs in the majority of patients. The most common complaint is chronic

[1] Cholelithiasis is related to impaired bile salt absorption due to ileal disease, with a consequent increase in cholesterol concentration in the bile and its precipitation in bile.

abdominal pain that is non-specific in character and location; it is often cramping and occurs in the right lower abdominal quadrant. Some patients complain of *'gola'* formation and others complain of a chronic diarrhea. When strictures involve the ileum and jejunum, the commonest mode of presentation is in the form of episodes of *subacute intestinal obstruction.* When the cecum is involved, a tender lump may be palpated in the right iliac fossa. Colonic tuberculosis, though uncommon, can mimic ulcerative colitis. The disease may present as malabsorption syndrome related to diminished mucosal absorptive area, lymphatic involvement and a blind loop effect of strictures. Occasionally, the presentation may be with a complication of the disease. Acute intestinal obstruction can occur, especially in the hypertrophic forms of the disease, due to intestinal strictures. Intestinal perforation may also occur in 1–10 per cent cases. Whatever the presentation, systemic features such as fever, malaise, anorexia and weight loss are frequent.

Diagnosis Clinical examination during episodes of abdominal pain may reveal abdominal distension, tenderness, and exaggeration of bowel sounds suggesting intestinal obstruction. A simple test such a plain X-ray of the abdomen during episodes of abdominal pain may prove that the 'non-specific' pain is related to subacute intestinal obstruction if it shows dilated small bowel loops with air fluid levels.

The two useful investigative modalities include a small bowel barium evaluation and colonoscopy. Roentgenographic changes include separation and flocculation of barium throughout the small bowel (related to an accelerated transit time and a decreased tone), distorted mucosal folds, contraction and retraction of the cecum with a distorted incompetent ileocecal valve. Strictures may be seen in the small bowel. Calcified mesenteric lymph nodes and an abnormal chest X-ray may also aid in the diagnosis of intestinal tuberculosis.

If the colon is involved, colonoscopy may help in the diagnosis by the demonstration of mucosal erosions, deformities of the ileocecal valve and histologic evidence of granulomas (the latter being seen in colonoscopy-guided biopsy tissue).

Increased erythrocyte sedimentation rate is also frequently seen but is too non-specific to be of diagnostic utility. Serologic tests, which are still being developed, may be useful in the diagnosis of the disorder if shown to be both sensitive and specific.

Treatment Medical treatment follows the same chemotherapeutic guidelines as for pulmonary tuberculosis. Combinations of isoniazid (300 mg), rifampicin (600 mg) and ethambutol (15 mg/kg) can be used for 18 months. Short course chemotherapy with regimens using pyrazinamide may be used; therapy is administered for a duration of 6–9 months.

Surgical treatment (limited intestinal resection) is indicated for recurrent episodes of intestinal obstruction or for complications such as intestinal perforation.

KEY CONCEPTS

Ulcerative colitis

- Ulcerative colitis is an inflammatory disease of the large intestine. It is predominantly mucosal and typically *begins in the rectum.* There is pathologic evidence of *pseudopolyps, crypt abscesses* but there are no 'skip' lesions.
- The clinical features include diarrhea and rectal bleeding (with or without fever). The disease has a relapsing-remitting course.
- 25% of patients have extraintestinal symptoms; those which parallel the severity of intestinal disease include peripheral arthritis, episcleritis and skin lesions. Spondylitis and sacroiliitis do not parallel bowel disease.
- Diagnosis is by the sigmoidoscopic appearance combined with the biopsy features; exclude infective colitis with stool examinations and cultures. Barium examination reveals thumb printing and loss of haustra.
- *Mild* disease (<5 stools/day) is treated with sulfasalazine and topical steroids; *moderate* disease (5–10 stools/day) is treated with sulfasalazine and high doses of oral steroids (which are tapered); *severe* disease (>10 stools/day, fever, tachycardia, anemia) carries the risk of *toxic megacolon* and is treated with i.v. fluids, i.v. antibiotics, and i.v. steroids. Avoid opiates and anticholinergics. Maintenance after an attack is with sulfasalazine; consider surgery for severe disabling disease, and for toxic megacolon not resolving despite 48 hours of medical treatment.
- There is an increased risk of colorectal cancer (more in pancolitis, upto 30% at 30 years) and periodic colonoscopic surveillance (with multiple biopsies) is recommended.

Crohn's disease

- Crohn's disease is a *transmural* inflammation affecting the terminal ileum and colon, but usually *sparing the rectum.* There is pathologic evidence of *cobblestoning,* along with 'skip' areas, and *non-caseating granulomata.* Fistula formation is typical.
- Presentation may be with abdominal pain, non-bloody diarrhea, or with RLQ abdominal mass. The perianal disease is accompanied by fistula formation.
- Extraabdominal disease may be present as in ulcerative colitis; peripheral arthritis, uveitis and skin lesions parallel bowel disease activity, whereas spondylitis-sacroiliitis do not.
- Barium examination reveals the *string sign,* and ileal strictures with rectal sparing. Colonoscopic biopsy may reveal granulomas.
- Management principles are similar to those for ulcerative colitis but drugs are generally less effective. Oral sulfasalazine may need to be supplemented with immunosuppressive agents. Metronidazole is useful for perianal disease and fistulae. Corticosteroids are useful for acute exacerbations. Surgery is usually performed for complications of the disease.

Intestinal tuberculosis

- Intestinal tuberculosis may be *primary* (ingested tubercle bacillus, bovine or human) or *secondary* (swallowing sputum laden with tubercle bacilli in a patient with pulmonary disease).
- The disease may be *ulcerohypertrophic* or *ulceroconstrictive* in appearance. Strictures are frequently present. The *ileocecal region* is preferentially involved due to a greater stasis of contents, and due to the presence of prominent lymphatics in the gut wall; the mesenteric nodes may be involved.
- The clinical presentation is varied: '*gola*' formation is common and is related to episodes of *subacute intestinal obstruction;* other manifestations include diarrhea, malabsorption syndrome and a palpable RLQ mass. Potential *complications* include GI hemorrhage, perforation, and intestinal obstruction.
- The diagnosis is suggested by the typical radiologic appearance in a barium meal follow-through; tissue diagnosis requires biopsy.
- The treatment consists of chemotherapy with standard ATT drugs. Surgery may be necessary for complications such as strictures (intestinal obstruction) or acute perforation.

13.7 Hepatitis

ACUTE VIRAL HEPATITIS

Hepatitis A

Virology Hepatitis A is a 27 nm, non-enveloped single stranded RNA virus with properties of the enterovirus genus of the picorna virus family. It is the only hepatitis virus that has been cultivated in vitro. It is non-cytopathic and is capable of growth in several epithelial cell lines.

Epidemiology The hepatitis A virus is spread by the feco-oral route. Sporadic cases result from a person-to-person transmission whereas epidemics are usually related to water or food contamination. The virus appears in the feces of patients for upto two weeks prior to the onset of jaundice and other clinical manifestations. Fecal excretion may continue thereafter for a week. Hence, a person is at risk of transmitting the virus in the incubation period itself. Intrafamilial spread is common.

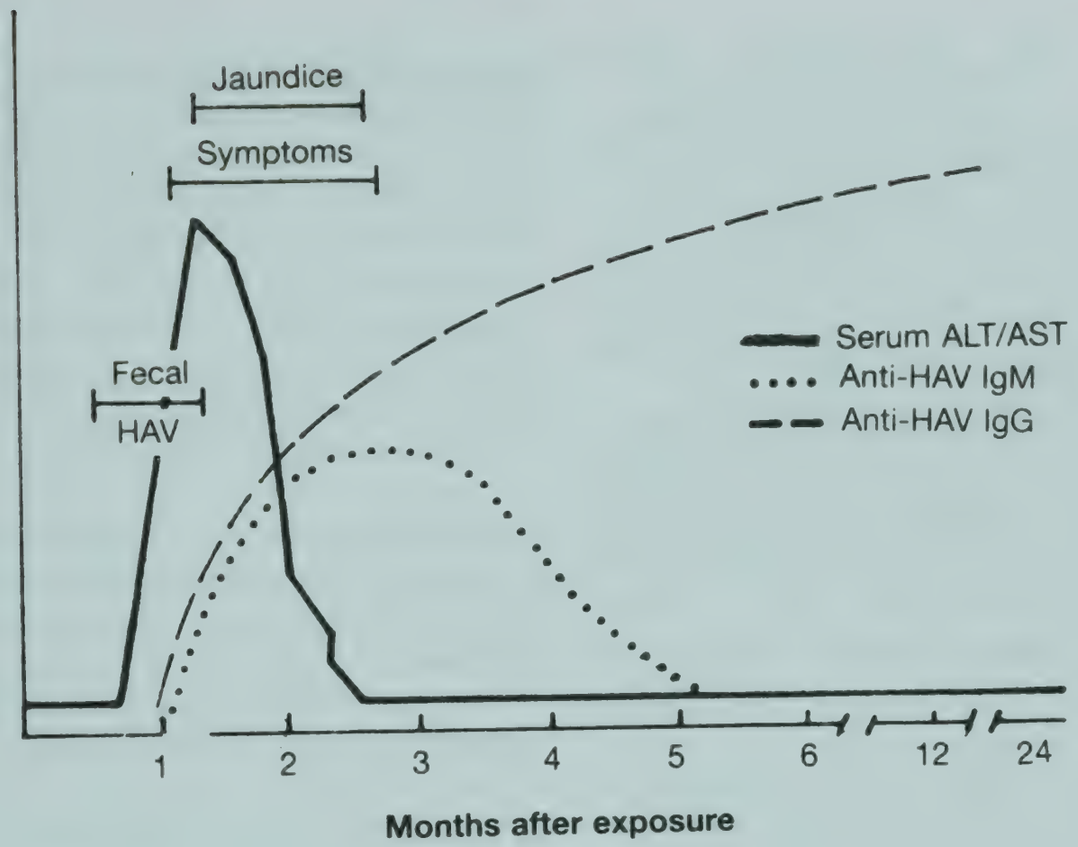
Pathology The typical lesions of viral hepatitis include hepatocyte ballooning and necrosis with formation of acidophilic bodies (hepatocytes with condensed cytoplasm and pyknotic nuclei), and a mononuclear cell infiltrate.

Clinical features The clinical profile of viral hepatitis is triphasic. There is an initial *prodromal illness* lasting for 2–5 days. It is characterised by anorexia, nausea, malaise and mild fever. There may be mild pain in the right upper quadrant of the abdomen. The fever is never hectic and the abdominal pain is rarely severe. Vomiting may occur and can be severe. This is followed by the *icteric phase* with the onset of clinical jaundice, dark-coloured urine and light-coloured stools. Upto 50 per cent of cases of viral hepatitis may be anicteric, that is, without clinical jaundice. The liver is usually palpable and mildly tender. In 20 per cent of cases the spleen is just palpable. The *recovery phase* is characterised by gradual resolution of symptoms and laboratory tests.

Diagnosis The serum transaminases are typically elevated (>3 times normal) as is the serum bilirubin (in icteric cases). The IgM anti-HAV antibody develops early in the course of the disease and the IgG anti-HAV antibody rises over the next 2–3 months (Fig 13.15).

Therapy and course Therapy is supportive and includes ensuring adequate hydration and caloric intake. Hepatitis A does not lead to chronic disease or a carrier state.

Prophylaxis Post-exposure prophylaxis is with immune serum globulin (0.02 ml/kg) given intramuscularly within two weeks of exposure and is recommended for household and sexual contacts. Pre-exposure prophylaxis can be given to travellers to endemic areas. Recently an inactivated viral vaccine has been approved for use.



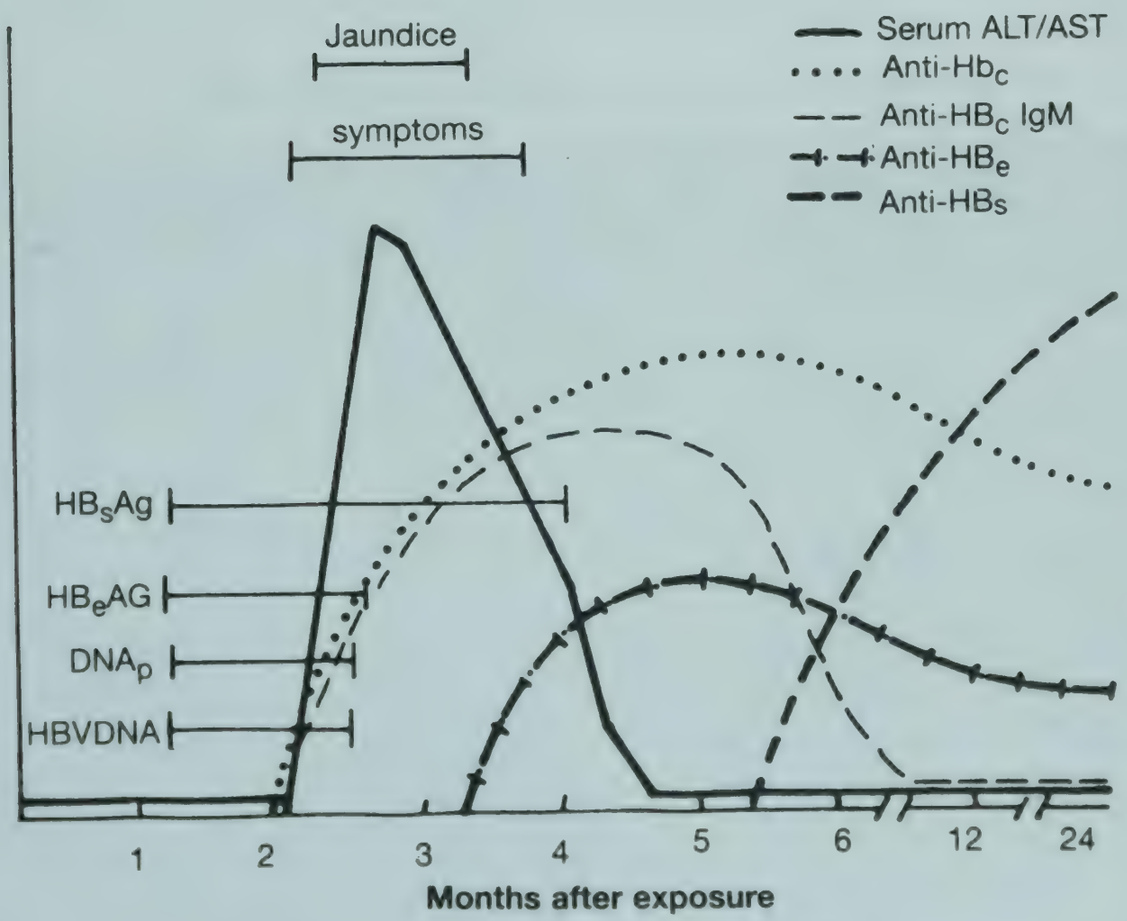


Fig 13.15 Serologic profile of viral hepatitis
a. Hepatitis A
b. Hepatitis B

Hepatitis B

Virology The hepatitis B virus is a double-shelled DNA virus with a single circular DNA molecule and with an endogenous DNA polymerase. It belongs to the new class of 'hepadna viruses'; viruses in this category replicate through an RNA intermediate that requires the enzyme reverse transcriptase.

The genome of the hepatitis B virus contains distinct parts which code for different proteins. Thus, the S gene encodes the hepatitis B surface antigen (HB_SAg), the C gene codes for the core antigen (HB_CAg) and the E antigen (HB_eAg), the P gene encodes polymerase and the X gene encodes a protein necessary for viral replication.

The hepatitis B virus is an oncogenic virus which integrates into the host genome and may lie dormant for several years before initiating carcinogenesis.

Epidemiology Hepatitis B is transmitted percutaneously either by blood transfusion, intravenous drug abuse, accidental needlestick injury or by sexual contact. Tattooing with contaminated instruments or shaving with a contaminated razor are the other modes of transmission. The virus can be transmitted transplacentally in utero. It is estimated that there are 43 million carriers in India, 10 per cent of whom are highly infective.

Clinical features The clinical features of hepatitis B are similar to that of hepatitis A except for the greater incidence of a serum sickness-like syndrome in the prodromal phase (10–20 per cent) characterised by urticaria, polyarthralgia and a transient rash.

Diagnosis The presence of HB_SAg in serum establishes infection with the virus but does not distinguish disease from a carrier state. An early

Table 13.12 Comparison of agents causing viral hepatitis

	Type of hepatitis				
	A	*B*	*C*	*D*	*E*
1. Etiology	Picorna virus (SS RNA)	Hepadna virus (DNA ARC)	Flavivirus (SS RNA)	RNA virus (SS RNA)	RNA virus (SS)
2. Age group affected	childhood	all	all	all	adults
3. Transmission routes					
Oral	+	?	?	?	+
Percutaneous	rare	+	+	+	-
Sexual	±	+	-	+	?
4. Incubation period (days)	30	50–150	50	60–90	40–50
5. a. Anicteric presentation	uncommon	common	-	common	not uncommon
5. b. Rash, arthralgias	-	+	-	-	+
6. Serologic markers	+	+	+	+	+
7. Chronic carrier state	-	+	+	+	-
8. Chronic disease state	-	+	++	++	-
9. Mortality	low	low	low	high	moderate
10. Availability of prophylactic serum/vaccine	+	+	?	prevent hepatitis B	?

rise of anticore antibodies (HB_cAg) or a later rise of antibody to HB_sAg indicate infection (with immunity being reflected by the latter). The presence of HB_eAg identifies active viral replication (Fig 13.15).

Treatment and sequelae There is no specific treatment other than general supportive measures. A persistent carrier state can develop in 2–8 per cent of adults and in upto 20 per cent of children. Fulminant hepatitis may occur in 1–2 per cent of cases. Chronic hepatitis may also develop and can lead to cirrhosis in 25–30 per cent of cases.

Prophylaxis The cornerstone of care is prevention of HBV infection with immunoprophylaxis. Postexposure prophylaxis employs the use of hepatitis B immune globulin within 24 hours of exposure and hepatitis B vaccine within one week of exposure. Pre-exposure prophylaxis is by vaccination of healthcare personnel such as dialysis patients, staff and medical personnel with frequent exposure to blood products, who are at risk. It has been suggested that the most cost effective method of disease prevention may be the routine vaccination of all children. The recombinant vaccine can be given as 3 doses (20 µg each) at 0, 1 and 6 months administered intramuscularly into the deltoid or subcutaneously.

Hepatitis C

Epidemiology Hepatitis C virus is the commonest cause of posttransfusion hepatitis. It has also been identified as a cause of sporadic cases of acute viral hepatitis.

Virology Hepatitis C virus is a 30–60 nm virus of the genus flavivirus (in the family of arboviruses). It is a single stranded RNA virus. An assay for anti-HCV has permitted identification of antibodies to the virus. Since the production of antibodies may take 5–20 weeks after onset of symptoms, this assay serves mainly to detect chronic infection.

Clinical features The mode of exposure to the virus is by blood transfusion, accidental needlestick or with parenteral drug abuse. The majority of infections tend to be clinically asymptomatic. Liver enzymes (transaminases) are typically elevated and characteristically fluctuating. Persistent elevation of transaminases for more than six months occurs in 50–70 per cent of patients. Acute hepatitis C has a striking propensity to become chronic. A chronic carrier state is well-recognised. Other long term complications include cirrhosis and hepatocellular carcinoma.

Treatment There is no established immunoprophylaxis for hepatitis C. Preliminary studies show that the treatment of acute or chronic hepatitis C with alpha interferon (1–3 million IU subcutaneously three times a week) results in an improvement in hepatic histology and in biochemical tests.

Hepatitis D

Epidemiology Delta hepatitis or hepatitis D infection occurs either as a concomitant infection with hepatitis B or as a superinfection (delta hepatitis in a chronic HB_sAg carrier). In developing countries it is associated with the frequently-found chronic carrier states of hepatitis B. In developed countries, it occurs among drug addicts and hemophiliacs.

Virology Hepatitis D virus or the delta agent is a unique RNA virus that resembles plant satellite viruses. It is a defective virus with a circular molecule of negative polarity, single stranded RNA that depends for its replication on the concomitant presence of hepatitis B virus for 'helper function'.

Clinical features Delta hepatitis can be an acute or a chronic hepatitis with the latter frequently leading to hepatic cirrhosis. The diagnosis is established by demonstrating the delta antigen in serum as well as antidelta

antibody; IgG and IgM antibodies in a rising titre indicate acute infection, where as sustained high IgM antibodies titres indicate chronic infection.

Treatment The preventive measures against delta hepatitis are the same as those for the prevention of hepatitis B infection.

Hepatitis E: Enteral non-A non-B Hepatitis

Epidemiology The first epidemic of hepatitis E virus infection was reported in 1955 when drinking water was contaminated by overflow from an open sewer in Delhi. About 29,300 residents developed a benign self-limited acute hepatitis. Of ten Indian hepatitis epidemics investigated so far, nine have been found to be due to enteric NANB hepatitis (hepatitis E virus). The largest epidemic occurred in 1991 and affected an estimated 79,000 people in Kanpur, India.

Virology and pathology Hepatitis E virus has been identified as a 27–32 nm virus-like particles by immune electron microscopic studies of stools of cases. It is a positive strand RNA virus. Recently an antigen related to HEV (HEV Ag) has been identified and a specific anti-HEV Ag antibody has been developed.

Pathologically, hepatitis E is characterised by prominent cholestasis with marked canalicular and intracellular bile stasis. There is a moderate 'mixed' (mononuclear and polymorphonuclear) leucocytic infiltration of the portal and intralobular regions with prominent lipofuscin pigment within the Kupffer cells.

Clinical features The clinical features are quite similar to hepatitis A infection. The attack rate is around two per cent, being higher in young adults than in children. The attack rate is much higher (20 per cent) in pregnant women. In pregnancy, this otherwise benign infection tends to run a severe course frequently resulting in 'fulminant hepatic failure'; the mortality in pregnancy may be 10–20 per cent. There are no chronic sequelae of the disease. Intrafamilial spread was not present in the Kanpur epidemic.

Treatment and control The treatment is purely supportive and control of the disease requires ensuring a supply of clean water and adequate sanitation. There is no available vaccine or immunoprophylaxis at present.

SEQUELAE OF HEPATITIS

Chronic Hepatitis

Chronic hepatitis is defined as persistence of diffuse hepatic inflammation as evidenced by clinical symptoms, biochemical tests or liver biopsy findings beyond a period of six months after an episode of acute hepatitis.

Pathology A needle biopsy of the liver is needed for the diagnosis and classification of chronic hepatitis. *Chronic persistent hepatitis* is suggested by the presence of mononuclear cell infiltration in the portal area but with an intact limiting plate of hepatocytes surrounding the portal zone. *Chronic lobular hepatitis* is characterised by scattered necrosis throughout the hepatic lobule. *Chronic active hepatitis* shows portal zone inflammation but in addition there is necrosis of the limiting plate (*piecemeal necrosis*).

Chronic active hepatitis may feature *bridging necrosis* where the chances of progression to cirrhosis increases to 30–40 per cent.

Bridging necrosis is characterised by disintegration of the reticulin network resulting in collapse of the hepatic lobule. The collapsed bridge consists of hepatocytes which span the areas between the portal tracts, between the central veins and the areas extending from the portal veins to central veins.

Etiology Chronic hepatitis usually follows hepatitis B or non-A non-B infection.

Occasionally chronic hepatitis may be autoimmune in origin or may be seen with drugs (such as M dopa, INH, amiodarone) or Wilson's disease.

Diagnosis The patients may or may not be symptomatic and the laboratory tests show varying elevations of bilirubin, transaminases and alkaline phosphatase.

Treatment Subjects who have chronic active hepatitis presumably of an autoimmune etiology and who are HB_SAg negative benefit from high dose prednisone therapy or a combination regimen of prednisone and azathioprine. Initial trials of a-interferon have yielded beneficial results in HBV-related chronic active hepatitis provided coinfection with the delta agent is absent.

Subacute Hepatic Failure

Subacute hepatic failure is the clinical syndrome of subacute onset (6 weeks to 6 months) of signs of hepatocellular failure (edema, ascites, hypoalbuminemia) in addition to jaundice.

Etiopathogenesis Whereas hepatitis A virus does not cause this syndrome, hepatitis B causes the illness in 45 per cent, and non-A and non-B viruses (C, D, E) in 55 per cent of the cases encountered. Diabetics and middle-aged subjects seem more prone to this complication.

Pathology The liver biopsy shows features of acute viral hepatitis along with bridging necrosis. There may be *submassive necrosis* (severe bridging necrosis).

Clinical features Persistent jaundice after an episode of viral hepatitis along with the onset of peripheral edema and ascites after six weeks is the usual clinical picture. The serum transaminases are elevated and there is associated hypoalbuminemia and coagulopathies.

Treatment and prognosis There is no specific treatment other than general supportive measures. This condition is associated with a mortality rate of 80 per cent.

Fulminant Hepatic Failure

Fulminant hepatic failure refers to acute severe impairment of liver function lasting for less than four weeks, and accompanied by encephalopathy and coma.

Etiology Viral hepatitis accounts for more than 80 per cent of cases of fulminant hepatic failure. Hepatitis B and other non-A and non-B (C, D, E) viruses account for the majority of cases. Other causes include toxic hepatitis (ingestion of acetaminophen, white phosphorus or Amanita mushrooms) or Wilson's disease.

Pathophysiology Encephalopathy is the central manifestation of fulminant hepatitis. It is possibly multifactorial in etiology; cerebral edema, increased blood cerebrospinal fluid ammonia levels, increased GABA, mercaptans, false neurotransmitters in the brain and an altered blood-brain barrier are contributory mechanisms.

Diagnosis The diagnosis is established in a patient with severe hepatic failure who lapses into a coma over a period of hours or days.

Treatment and prognosis The treatment is mainly supportive with a view to maintaining hydration, electrolyte and acid-base balance, an adequate caloric intake, prompt correction of cerebral edema and prompt identification and treatment of any infection. The illness terminates fatally in 75–85 per cent of patients. Hepatic transplantation has been attempted in select patients and preliminary results are encouraging.

Alcoholic Hepatitis

Alcoholic hepatitis is defined as alcohol-induced inflammation of the liver; it is characterised by an inflammatory cell infiltrate and hepatocyte

necrosis, often accompanied by biochemical evidence of deranged liver function.

Pathogenesis and clinical features Alcohol is a well-known hepatotoxin. Alcoholic hepatitis is characterised by the ballooning degeneration of hepatocytes which are surrounded by a mixed cellular infiltrate comprising of both polymorphonuclear leucocytes and lymphocytes. The histological hallmark of alcoholic hepatitis is the presence of clumps of perinuclear eosinophilic material within damaged hepatocytes known as *Mallory bodies* (also called alcoholic hyaline). There may be collagen deposition around the central vein and in the perisinusoidal area: this is called *central hyaline sclerosis* and is a harbinger of future cirrhosis.

Clinically, acute alcoholic hepatitis presents as acute onset of fever (101–102°F), jaundice and right hypochondrial pain in an alcoholic who has been drinking heavily. The physical examination reveals an enlarged tender liver, and icterus.

Table 13.13 Drug-induced liver damage

Type of reaction	*Drugs implicated*	*Clinical picture*
Toxic hepatitis	Analgesics (acetaminophen), hydrocarbons (carbon tetrachloride), mushrooms (Amanita), metals (yellow phosphorus)	acute liver failure, acute onset of jaundice
Acute hepatitis (idiosyncratic)	Isoniazid, disulfiram, antithyroid (propylthiouracil)	like viral hepatitis
Acute hepatitis (allergic)	Halothane, phenytoin	as above + arthralgia, fever, rash, eosinophilia
Chronic hepatitis	Methyldopa, nitrofurantoin, isoniazid	resembles autoimmune chronic active hepatitis
Cholestatic jaundice	Antibiotics (erythromycin), anabolic steroids (methyltestosterone), oral contraceptives, phenothiazines (chlorpromazine)	jaundice with pruritus in the apparently well-preserved individual
Granulomatous hepatitis	Antiarrhythmics (quinidine group), diltiazem, anticonvulsants (carbamazepine), allopurinol, phenylbutazone	low-grade fever, chronic fatigue, jaundice
Cirrhosis	Methyldopa, methotrexate	like alcoholic cirrhosis
Ischemic necrosis	Cocaine	acute onset of jaundice along with shock, disseminated intravascular coagulation and myocardial injury
Veno-occlusive disease	Cyclophosphamide, herbal teas	acute onset of painful hepatomegaly, ascites, jaundice
Angiosarcoma	Vinyl chloride, thorium, arsenic	space-occupying hepatic lesion

Ascites, pedal edema and encephalopathy may be present in severe cases.

Investigations Leucocytosis may be present and usually indicates severe hepatitis. Variable degrees of hyperbilirubinemia and elevations of alkaline phosphatase are present. The biochemical hallmark is an elevation of the transaminases; AST (SGOT) is disproportionately elevated so that the ratio of AST/ALT is >2. The prothrombin time may be prolonged.

Treatment The treatment of alcoholic hepatitis is supportive. The use of either glucocorticoids or prophylthiouracil remains controversial despite the demonstration of benefit in some trials. If hepatitis is severe, a trial of glucocorticoids may be contemplated. The single most important advice is abstinence from alcohol. Biochemical and clinical recovery takes weeks, although the course may be more protracted on occasion.

Drug-induced hepatic damage

The active role of the liver in body metabolism places it at very high risk for injury by drugs that undergo hepatic metabolism. Drugs can injure various parts of the liver architecture, such as the hepatocyte, the bile canaliculi and sinusoidal cells, endothelial cells and the interstitium. Table 13.13 provides an overview of drug-related hepatic injury.

A careful history of drugs ingested is essential in any patient with jaundice. The temporal sequence of events – onset after ingestion of the drug and improvement after cessation of intake – helps support the diagnosis. The mainstay of treatment is stoppage of the offending agent. Acetylcysteine has proven useful in treating acetaminophen-induced hepatitis. Otherwise, there is no specific treatment. Rechallenge with the same agent is generally avoided unless the diagnosis of drug-related reaction is in doubt.

KEY CONCEPTS

Viral hepatitis

- At least six different viruses have been identified: *A* (picorna virus, feco-oral transmission via water), *B* (DNA virus, parenteral/sexual transmission), *C* (RNA virus, posttransfusion), *D* (δ agent; defective RNA virus coinfects hepatitis B), *E* (RNA virus, enteric transmission), and *G* (recently described).
- The *prodromal phase* is marked by anorexia, nausea and vomiting; hepatitis B infection may be associated with arthralgia-rash. Dark-coloured urine heralds the onset of the *icteric* phase. Jaundice and a palpable, slightly tender liver are important clinical features. The *complications* include fulminant hepatitis, subacute hepatic failure and chronic hepatitis.
- The diagnosis is suggested by the clinical picture in conjunction with laboratory evidence of elevated transaminases and bilirubin. Take care to exclude drug-related hepatitis. Establishing the specific viral etiology requires *serology*; Hepatitis A: HAV in stools, or IgM anti-HAV in serum; Hepatitis B: HB_SAg, anti-HB_C, Hb_eAg; Hepatitis C: anti-HCV antibodies.
- The treatment is mainly supportive. Avoid alcohol and hepatotoxic drugs. Bed rest and adequate caloric intake are important. Corticosteroids have no role.
- Preventive measures include vaccination (hepatitis A and B) and screening (for hepatitis B and C) in blood banks. It has been recommended that hepatitis B vaccination be incorporated into the Expanded Programme of Immunisation.

Chronic hepatitis

- When LFTs (elevated transaminases) remain deranged for >6 months after an episode of hepatitis, chronic hepatitis is present. It may be post-viral hepatitis (hepatitis A does not cause chronic disease), or autoimmune (in young women; associated with HLA DR3, B8) in origin.
- Signs of liver cell disease dominate the clinical picture and include fatigue, malaise and jaundice. Laboratory evidence of elevated transaminases is usually present.

The autoimmune variety is associated with positive ANA or anti-smooth cell antibody. Chronic hepatitis (post-viral) can be *chronic persistent hepatitis, chronic lobular hepatitis,* or *chronic active hepatitis.*

➢ Clinically these three are indistiguishable but appearance on the liver biopsy is distinctive. CPH: *portal triaditis.* CLH: portal + lobular inflammation. CAH: portal triaditis + *piecemeal necrosis* + *bridging necrosis.*

➢ The autoimmune type is best treated with corticosteroids with azathioprine. CAH due to hepatitis B is treated with α-interferon and vidarabine. CAH due to hepatitis C is treated with α-interferon.

Drug-induced hepatitis

➢ Drug-induced hepatitis can be due to *direct toxicity* (e.g. carbon tetrachloride; short latency, predictable response in dose dependent fashion) or an *idiosyncratic* response (e.g., INH, halothane, chlorpromazine; variable latency, unpredictable onset with no dose-response relation; may be associated with arthralgia, rash and eosinophilia).

13.8 Cirrhosis and portal hypertension

CIRRHOSIS

Cirrhosis is defined as the occurrence of irreversible fibrous scarring of the liver along with hepatocellular regeneration that takes the form of nodules. It is the response of the liver to a variety of inflammatory, toxic, metabolic and congestive insults.

Etiology and pathology When the regenerative nodules are small (<3 mm) the term *micronodular* cirrhosis is used. This is a typical pathologic feature of alcoholic cirrhosis. When the nodules are large (>3 mm) the term *macronodular* cirrhosis is used. The latter is very commonly seen as a sequel of chronic active hepatitis when it is called *postnecrotic* cirrhosis. The causes of cirrhosis are listed in Table 13.14. Postnecrotic cirrhosis is the commonest type of cirrhosis in the third world, whereas alcoholic cirrhosis is the commonest variety encountered in the developed countries. The liver is usually shrunken in end stage cirrhosis, though it may be enlarged in alcoholic cirrhosis due to associated fatty infiltration.

Pathophysiology and clinical features The clinical manifestations of cirrhosis are due to disruption of hepatocyte function and of hepatic architecture. In the stage of 'well-compensated' cirrhosis, the affected individual is often asymptomatic with little clinical evidence of hepatocellular dysfunction. As clinical evidence of complications develop, particularly signs of hepatocellular dysfunction, the 'decompensated' phase of cirrhosis begins to manifest. The fibrous scarring and disruption of normal hepatic architecture leads to portal hypertension and intrahepatic vascular shunting. The two attendant complications of portal hypertension are variceal hemorrhage and splenomegaly (often with hypersplenism). Ascites may develop which may be complicated by infection of the peritoneal cavity: this is known as *spontaneous bacterial peritonitis*.

Table 13.14 Causes of hepatic cirrhosis

Common
Postnecrotic cirrhosis (post-B or non-A, non-B hepatitis)
Alcoholic liver disease
Cryptogenic
Uncommon
Drugs: Methotrexate, M-dopa, amiodarone
Biliary cirrhosis
Budd-Chiari syndrome
Chronic right-sided heart failure
Wilson's disease
Hemochromatosis
Galactosemia
α_1-antitrypsin deficiency

PORTAL HYPERTENSION

Portal hypertension is defined as an increase in the hydrostatic pressure within the portal vein or its tributaries. Since normal portal pressure

varies from 7–15 mmHg (corresponding to 10–20 cm saline), a pressure more than 18 mmHg parentheses around (corresponding to 10-20 cm saline) is taken as indicative of portal hypertension.

Pathophysiology and etiology The portal venous system is a valveless system beginning with the formation of the portal vein by the union of the superior mesenteric vein and the splenic vein behind the head of the pancreas, and terminating in the hepatic sinusoids. Normally the vascular resistance in the hepatic sinusoids is minimal. Portal hypertension can occur either due to an increased resistance to portal flow or due to a massive increase in portal blood flow itself. The latter usually causes only a mild increase in portal venous pressure. The causes include massive splenomegly—idiopathic or due to myeloproliferative disorders; such a mild increase is clinically not very relevant. Most clinical portal hypertension is, therefore, related to an increased resistance to portal venous blood flow. This resistance may be due to abnormalities anywhere along the portal venous system. Conceptually it is easier to classify the causes as *presinusoidal*, *sinusoidal* or *postsinusoidal*. Presinusoidal causes include extrahepatic causes (portal vein thrombosis) and intrahepatic causes (schistosomiasis, non-cirrhotic portal fibrosis). Cirrhosis of the liver is the prototype of sinusoidal hypertension. The cirrhotic nodules cause distortion and mechanical obstruction of the portal vascular bed. Postsinusoidal portal hypertension includes intrahepatic causes (nodular variety of non-cirrhotic portal fibrosis, veno-occlusive disease) and extrahepatic causes (Budd-Chiari syndrome, or suprahepatic inferior vena cava obstruction). This elevation of portal pressure may exist with or without elevation of sinusoidal pressure.

The major clinical manifestations of portal hypertension are upper gastrointestinal bleeding, ascites, splenomegaly and hepatic encephalopathy. Of these, variceal bleeding is related to the retrograde flow of high pressure portal venous blood into the low pressure systemic venous circulation at the sites of 'portosystemic anastomosis', especially those at the cardio-esophageal junction. Other veins which become engorged include abdominal wall collaterals and periumbilical veins which radiate from the umbilicus outwards (forming the *caput medusae*). The flow of blood along a patent umbilical vein (opening into the left branch of the portal vein) may itself generate a venous murmur known as the *Cruveilhier-Baumgarten murmur*. Both the caput medusae and the murmur indicate elevated pressure in the portal vein beyond the entry of the umbilical vein, that is, they are seen in intrahepatic portal hypertension and are absent in presinusoidal extrahepatic portal hypertension. The varices tend to get engorged and may rupture due to erosion or over-dilatation; this results in upper gastrointestinal hemorrhage. This is the most important complication of portal hypertension accounting for most of the mortality. Splenomegaly of a varying degree is universal in portal hypertension; it is mainly a congestive splenomegaly due to raised venous pressure. The spleen weighs about one kg on an average. *Hypersplenism* (which is defined as splenomegaly with pancytopenia and a hyperactive bone marrow) may occur in upto a third of patients. These abnormalities may be reversed with splenectomy.

The presence of ascites is related to the presence or absence of sinusoidal hypertension. Hepatic sinusoids are specialised capillaries with a fenestrated endothelium and no basement membrane. Being freely permeable to albumin, fluid exchange between the sinusoid and the interstitium is mainly influenced by hydrostatic pressure. Raised sinusoidal venous pressure results in increased output of lymph from the sinusoidal lumen to the space of Disse (for every 1 mmHg elevation in intrasinusoidal pressure, lymph output increases 60 per cent). This results in increased flow in liver lymphatics and direc

passage of lymph from the liver surface into the peritoneal cavity. This condition is known as a *weeping liver*. In presinusoidal hypertension there is no ascites. This is because the raised portal pressure is transmitted to the splanchnic capillaries which are quite different from hepatic sinusoids. Raised pressure in these capillaries is associated with reflex contraction of smooth muscle cells in the arteriolar wall and a reduction in their filtration coefficient. This process is known as intestinal microvascular auto-regulation. Further the intestinal interstitium is more compliant and the lymphatics more efficient in removing any intestinal edema. Consequently, transudation of lymphatic fluid is less, and when it occurs it is into the intestinal lumen and not into the peritoneal cavity.

Portosystemic encephalopathy defined as an abnormality of brain function due to liver disease, is yet another complication of portal hypertension. Since hepatocyte function is virtually normal in presinusoidal portal hypertension, encephalopathy is not a feature of this entity.

The etiology of portal hypertension varies from country to country. Thus, in the USA the commonest cause is cirrhosis of the liver (95 per cent) while in Egypt it is schistosomiasis. In India, non-cirrhotic portal fibrosis, extrahepatic portal venous obstruction and hepatic cirrhosis each account for roughly a third of cases. Hepatic venous outflow tract obstruction is also a common cause in India.

Treatment Therapeutic measures for portal hypertension are directed at attempts to lower portal venous pressure by medical or surgical means and measures to prevent recurrent variceal hemorrhage. Propranolo a non-specific beta-adrenergic blocker, reduces portal venous pressure when administered to patients with cirrhosis. Long term administration of propranolol (at a dose that reduces the heart rate by 25 per cent) has been shown to also reduce recurrent variceal hemorrhage. Surgical attempts to lower portal venous pressure have been based on the creation of an anatomic shunt between the high pressure portal venous system and the low pressure systemic venous system.

Non-selective shunts like the *portacaval shunt* (distal portal vein to the inferior vena cava) decompress the entire portal system. Though this does prevent recurrent variceal hemorrhage, the procedure totally diverts portal venous flow from the liver and consequently produces a high incidence of hepatic encephalopathy by adversely affecting hepatic function. Selective shunts like the *distal lienorenal shunt* are favoured in India as more than 50 per cent of patients with portal hypertension have extrahepatic obstruction. The lienorenal shunt procedure involves splenectomy and end-to-side anastomosis of the splenic vein into the renal vein close to the hilum of the kidney. In one of the modifications which preserves the spleen, the coronary vein, through which blood flows from the portal vein into the gastroesophageal varices, is ligated. Blood then flows from the varices via the short gastric veins to the splenic vein and then to the renal vein (*Warren shunt*). Splenectomy and a lienorenal shunt is preferred in India as the average splenic weight in patients is one kilogram and hypersplenism of a variable degree frequently coexists. The incidence of encephalopathy is less frequent after lienorenal shunts. It must be emphasised that in patients with cirrhosis, shunt surgery prevents recurrent variceal bleeding but does not prolong survival.

The most widely employed technique for preventing bleeding from varices in patients with cirrhosis is however, *endoscopic sclerotherapy* (EST). EST is used for both stopping hemorrhage in patients with actively bleeding varices as well as prophylactically to prevent recurrent bleeding. In repeated sclerotherapy sessions the varices are injected with a sclerosant solution which obliterates varices. Complications of EST include esophageal strictures and perforation of the esophageal wall. *Band ligation* of varices is an alternative to EST.

Disorders causing Portal Hypertension

Non-cirrhotic portal fibrosis (idiopathic portal hypertension)

Non-cirrhotic portal fibrosis is, as the name suggests, a disorder characterised clinically by portal hypertension with preserved hepatocyte function, and histopathologically by fibrosis of the portal tracts.

Epidemiology Non-cirrhotic portal fibrosis is very common in India and Japan. Similar cases have, however, been described from all over the world. It is a disease affecting young adult males in India, although in Japan there is a female predominance. Most patients belong to the middle socioeconomic class. It is widely prevalent in India.

Pathology and etiopathogenesis The exact etiology of the disease is not known. Infections (such as malaria) and toxic substances (arsenic, vinyl chloride) have been propounded as possible causative factors but there is no convincing evidence that they play any role.

The liver appears grossly normal, though it is firmer in consistency. The microscopic changes include an irregular fibrosis in the portal tracts, thrombotic occlusion and subintimal thickening of the medium-sized portal vein branches and perisinusoidal fibrosis (in the space of Disse). It is not clear as to which one of these is the primary abnormality. The hepatocyte architecture is maintained and the central veins are normal. A *nodular* variant has been described in which some parenchymal distortion occurs. The elevated vascular resistance exists at the level of intrahepatic portal venous radicles.

Clinical features The patient, usually a young adult, may present with an asymptomatic lump in the left hypochondrium, of several years duration. Splenomegaly is typically massive (average of 9 cm below costal margin). The other mode of presentation is with an episode of upper gastrointestinal hemorrhage (variceal bleeding). These patients typically bleed frequently and profusely. They tolerate their bleeds very well and only rarely do the episodes trigger off ascites or encephalopathy (these complications may occur in the nodular variant). The physical examination does not reveal any stigmata of liver failure such as icterus, spider nevi or red palms. There is usually a mild firm hepatomegaly, except in the nodular variant where the liver is shrunken (and hence, impalpable). The presence of moderate to massive splenomegaly is an essential requirement for the diagnosis. Ascites is absent except in the nodular variant where there is significant sinusoidal hypertension due to compression and distortion of sinusoids.

Investigations Liver function tests are often normal or reveal minor elevation in transaminase levels. A barium swallow or an endoscopy reveals the presence of esophageal varices. Either test can be used as they are equally accurate. Earlier, splenoportovenography was used to demonstrate patency of the portal vein and establish the peripheral subcapsular pruning of portal venous radicles (*withered tree* or *tree in winter* appearance). With the advent of ultrasonography, the size of the portal vein can be measured and Doppler ultrasound can characterise the flow in the portal vein (and hence assess its patency). A liver biopsy may be important to differentiate the disorder from cirrhosis. Liver biopsy, when taken with a minilaparotomy, must be a deep wedge biopsy, since in a superficial wedge biopsy subcapsular fibrosis may mimic cirrhosis.

Treatment Since these patients bleed frequently and the commonest cause of mortality is an episode of gastrointestinal hemorrhage, surgery (portacaval shunt) is probably the best therapeutic option. Liver function being normal, they tolerate surgery very well.

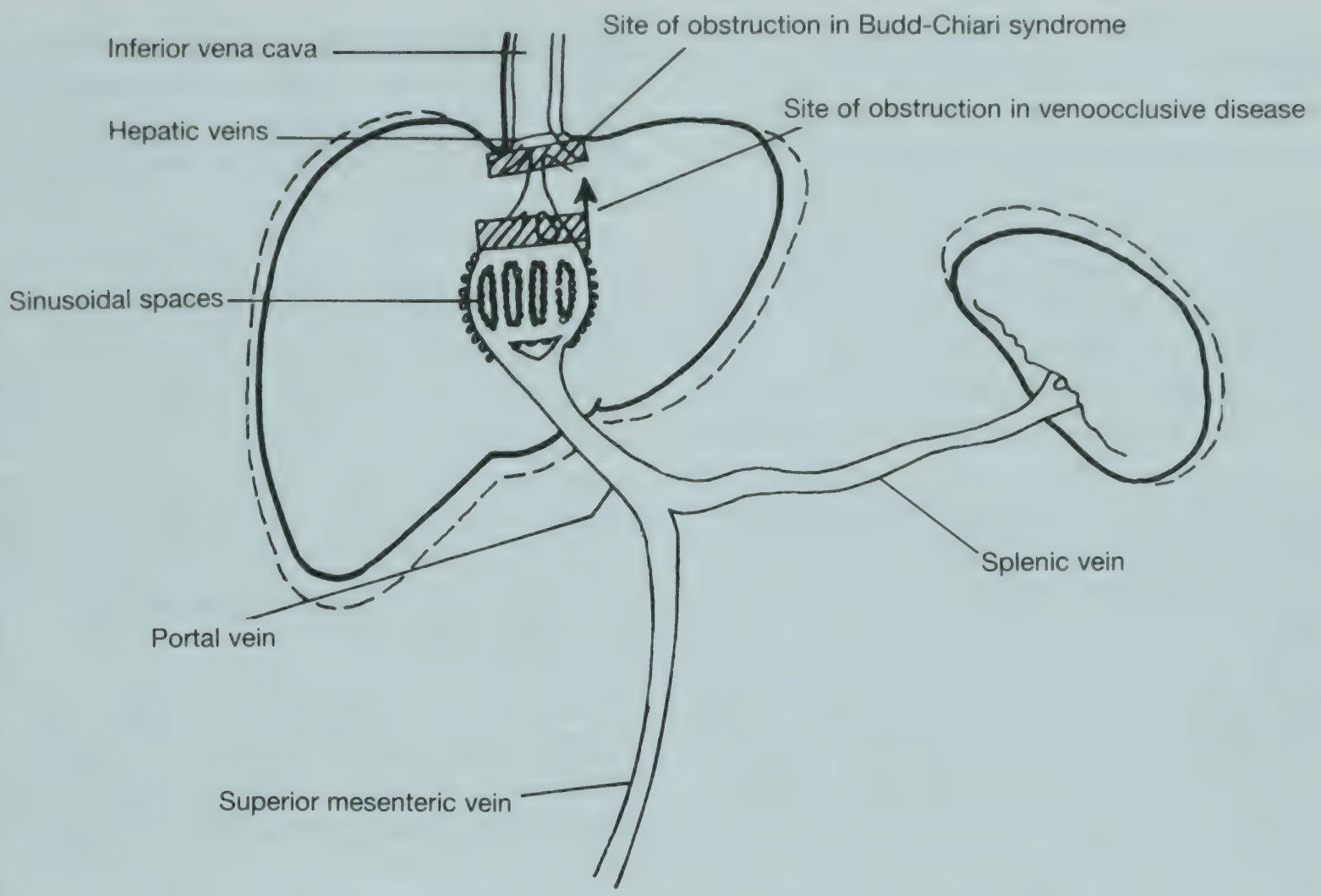


Fig 13.16 Levels of hepatic venous outflow tract obstruction

Hepatic venous outflow obstruction

The venous outflow from the liver to the right side of the heart includes the central veins in the lobules of the liver, small and medium-sized intrahepatic venous radicles, the right and left hepatic veins and the suprahepatic part of the inferior vena cava. An obstruction can occur anywhere along this tract; obstruction at the level of the small intrahepatic veins and central veins is called *venoocclusive disease.* Obstruction of the main hepatic veins and/or the suprahepatic inferior vena cava is called the *Budd-Chiari syndrome* (Fig 13.16).

Epidemiology and etiology Epidemics of venoocclusive disease have occurred in central India (Madhya Pradesh) and Afghanistan. The Indian epidemic has aptly demonstrated the adverse effects of the rural and tribal agricultural practice of cultivation and consumption of toxic herbs. In 1973 and in 1976, there were epidemics of venoocclusive disease in the Sarguja district of north Madhya Pradesh. This was due to contamination of the staple dietary cereal (Gondhli) with seeds of a wild plant (Jhunjunia, Crotolaria species) which have toxic *pyrrolizidine alkaloids* like monocrotolene. Occlusion of the main hepatic veins (Budd-Chiari syndrome) is most often idiopathic. It can also be secondary to myeloproliferative syndromes, hypercoagulable states or may occur as a complication of mass lesions in the liver as in a hepatic abscess or a malignant tumour. A few cases of hepatic venous outflow obstruction are related to suprahepatic membranous obstruction of the inferior vena cava, also called *coarctation of the vena cava.*

Pathology Obstruction of the inferior vena cava is characterised by marked dilatation of the sinusoids, a dilated central vein with some surrounding hemorrhage. Venoocclusive disease

is characterised by centrizonal necrosis and a *'creeping'* fibrosis associated with occlusion of the central hepatic vein, due to thrombosis, subendothelial edema or collagenisation.

Pathophysiology The number of hepatic veins occluded and the suddenness of their occlusion determine the clinical manifestations of the disease. The blocked venous outflow causes passive venous congestion of the liver and massive back-pressure necrosis of the hepatocytes. Acute occlusion causes sudden rapid distension of the liver (tender hepatomegaly), nausea, vomiting, ascites, signs of hepatocyte failure and occasionally circulatory collapse.

Gradual occlusion of the hepatic veins leads to a progressive hepatomegaly and manifestations of portal hypertension. Since recanalisation of thrombosed hepatic veins is very uncommon, the disease has a bad prognosis and a high mortality.

Clinical features It may be difficult to clinically differentiate venoocclusive disease from the Budd-Chiari syndrome, although there are some useful clinical pointers. Both disorders present with portal hypertension and ascites. Venoocclusive disease often has an acute onset with right upper quadrant abdominal pain, fever, mild jaundice and prominent ascites.

The Budd-Chiari syndrome can be of acute onset but is more often chronic, with a clinical presentation with prominent collaterals over the back, chest and flanks, pedal edema (if the intrahepatic inferior vena cava is involved) and upper gastrointestinal bleeding. Hepatomegaly and splenomegaly may be present in both disorders.

Investigations Liver function tests reveal some minor abnormalities of transaminases and alkaline phosphatase. Serum bilirubin may be elevated mildly. Ascitic fluid is most often a transudate but occasionally can be an exudate too. Varices are demonstrated with either a barium swallow or endoscopy. Ultrasonography is very useful in the diagnosis of hepatic venous outflow obstruction. Thus, if two or more major hepatic veins are not seen or their confluence and drainage into the inferior vena cava is not seen, venoocclusive disease or major hepatic venous obstruction is likely. The inferior vena cava is patent and the caudate lobe of the liver is enlarged in these cases. Narrowing of the inferior vena cava (supra- or intrahepatic part) with proximal dilatation and dilated hepatic veins suggests the diagnosis of inferior vena cava obstruction. Inferior vena cavography and hepatic venography will also establish the site of hepatic venous outflow obstruction. A liver biopsy may suggest venoocclusive disease but it may be non-diagnostic.

Prognosis The prognosis is very good for membranous inferior vena cava obstruction, intermediate for obstruction of major hepatic veins, and poor for patients with venoocclusive disease.

Treatment Medical treatment is not very satisfactory and includes the management of bleeding varices, ascites and liver failure. Acute Budd-Chiari syndrome due to thrombotic occlusion of the hepatic veins or the inferior vena cava can be treated with a thrombolytic agent (streptokinase or urokinase) followed by oral anticoagulation.

Membranous obstruction of the inferior vena cava has been treated both with surgical excision as well as, recently, with balloon angioplasty with gratifying results.

Chronic occlusions of major hepatic veins or of the inferior vena cava require a shunt procedure. When both hepatic veins and the inferior vena cava are obstructed, a *meso-atrial shunt* can be performed. When only the inferior vena cava is blocked a *cavo-atrial* procedure seems appropriate. When only the hepatic veins are blocked a *portacaval shunt* is the procedure of choice. *Splenopneumoplexy* is an alternative operation for both hepatic venous obstructions and inferior vena cava. The spleen is mobilised

and brought into contact with the inferior surface of lungs through a hole made in the diaphragm with the expectation of developing venous collaterals between the systemic and portal circuit.

BILIARY CIRRHOSIS

Biliary cirrhosis is the chronic inflammation and fibrous obliteration of bile ducts associated with hepatic parenchymal fibrosis.

Etiology and pathology Biliary cirrhosis may be idiopathic *(primary)* or secondary to extra-hepatic biliary obstruction *(secondary)*. Primary biliary cirrhosis is an immunoinflammatory disease; there is immune-mediated damage of the bile ducts and serologic presence of antimitochondrial antibodies. Secondary biliary cirrhosis is related to longstanding obstruction of the extrahepatic bile ducts, usually related to gallstones, postoperative strictures or to sclerosing cholangitis.

Pathologically, primary biliary cirrhosis is initially characterised by necrotising destruction of medium and small bile ducts by inflammatory cells. This is soon followed by periductal granulomas and proliferation of the smaller bile ductules. Eventually the fibrosis extends from the portal triad into the hepatic parenchyma and cirrhosis (micro- or macronodular) develops. Secondary biliary cirrhosis has a similar pathologic picture but additionally there are prominent *'bile lakes'*—areas of extravasated bile—surrounded by pseudoxanthomatous cells.

Clinical features The clinical features of both the primary and the secondary forms of the disease are similar. Patients with secondary biliary cirrhosis usually have a history of obstructive jaundice of at least 6–12 months duration. Patients with primary biliary cirrhosis may have systemic features like Raynaud's phenomenon or the sicca syndrome (dry eyes and mucosa). These patients are also often women in the third to fifth decade of life.

Other clinical features include jaundice, pruritus, hyperpigmentation of the exposed areas of the skin, and xanthomas and xanthelasma. Impaired biliary excretion and consequent malabsorption of fat-soluble vitamins may manifest as bone pain (vitamin D deficiency), easy bruising (vitamin K deficiency), dermatitis (vitamin E malabsorption) and night blindness (hypovitaminosis A). Signs of portal hypertension are uncommon but do supervene late in the disease course.

Laboratory investigations Laboratory test abnormalities are similar in both the primary and seconday forms of the disease with one important difference: tests for anti-mitochondrial antibodies are positive in 90 per cent of patients with primary biliary cirrhosis but not in secondary biliary cirrhosis. Otherwise, there is evidence of conjugated hyperbilirubinemia, elevated alkaline phosphatase and 5' nucleotidase levels. Serum aminotransferase levels are modestly elevated and an abnormal serum lipoprotein (Lipoprotein X) may be detected. The biliary tract should be evaluated in every case to confirm (in the case of secondary biliary cirrhosis) or exclude (in the case of suspected primary biliary cirrhosis) obstruction.

Treatment In secondary biliary cirrhosis, therapeutic measures are directed towards relief of biliary obstruction either by surgical measures or by means of stenting procedures. Several drugs have been used for treating primary biliary cirrhosis. Glucocorticoids and D-penicillamine have been proven to be ineffective, whereas azathioprine and cyclosporine remain of questionable efficacy. Colchicine, methotrexate and ursodeoxycholic acid have been shown to have some benefit in select patients. General measures include supplementation of fat-soluble vitamins parenterally (Vitamins A, K) or orally (Vitamin D). Dietary substitution of medium-chain triglycerides, and the use of oral bile salt sequestrants (cholestyramine) to relieve pruritus are important adjunctive measures.

KEY CONCEPTS

Cirrhosis of the liver

- Hepatic cirrhosis comprises the *triad* of hepatocyte *necrosis* with reparative *fibrosis* and *nodular regeneration;* cirrhosis can be *micronodular* (nodules <1 cm) or *macronodular.* The causes of hepatic cirrhosis include alcohol intake, viral hepatitis (*postnecrotic cirrhosis*), hemochromatosis, glycogen storage disease and Wilson's disease.
- Symptoms may be due to hepatocyte dysfunction or due to portal hypertension (ascites, variceal bleeding). There is an increased risk of development of hepatic cancer. There is also a variable derangement of LFT.
- The clinical setting is usually suggestive but definitive diagnosis of cirrhosis requires a liver biopsy (which may not usually be necessary).
- Management is directed towards the treatment of portal hypertension (see below), and the prevention of further damage by alcohol (abstinence) or hepatotoxic drugs.

Portal hypertension

- This may be due to *increased portal flow* (rare; e.g. A–V fistula, conditions with massive splenomegaly) or due to *increased portal vascular resistance* (more common; e.g., distortion or compression of vasculature by cirrhotic nodules).
- It may be *presinusoidal* (prehepatic: portal vein thrombosis; intrahepatic: NCPF; usually with preserved liver function), *sinusoidal* (e.g. alcoholic cirrhosis; associated with deranged liver function), or *postsinusoidal* (intrahepatic: venoocclusive disease; post-hepatic: IVC obstruction; variable degrees of hepatic dysfunction).
- The symptoms may be due to *increased portal venous pressure* (ascites, varices at the site of portosystemic anastomosis) or due to *bypass of hepatic metabolic machinery* (encephalopathy).
- Ascites is related to the increased formation of lymph and renal retention of sodium and water. Treatment is with paracentesis. Spontaneous *bacterial peritonitis* has to be watched out for.
- Varices can be diagnosed with endoscopy or a barium swallow. Varices can bleed (hematemesis). The treatment options for acute variceal bleed include (besides volume replacement) sclerotherapy, vasopressin, or balloon tamponade. Chronic therapy for varices includes sclerotherapy, use of β-blocking drugs (to lower portal venous pressure), ligation or shunt surgery.
- Encephalopathy manifests as motor abnormalities (*flapping tremor*), with disturbed cognition and mentation. The treatment consists of reversing any precipitating cause (GI bleed, dietary indiscretion, diuretic overuse, infections), administering lactulose to reduce the protein load, and antibiotics to reduce production of ammonia by the gut flora.

Hepatic venous outflow obstruction

- Hepatic venous outflow obstruction can be at the level of hepatic *venules* (*venoocclusive disease*), or related to the *thrombosis* of hepatic veins or the IVC (hypercoagulable states), or due to *membranous obstruction* of IVC.
- HVO obstruction results in hepatic sinusoidal congestion, portal hypertension and a variable extent of hepatic dysfunction. The clinical presentation is with ascites, tender hepatomegaly, prominent abdominal wall collaterals and lower extremity edema (the latter in IVC obstruction).
- US is important for identifying an enlarged caudate lobe, and for assessing hepatic venous flow pattern with Doppler.
- The treatment depends on the etiology: balloon membranotomy for an IVC membrane and a portacaval shunt for hepatic venous obstruction (meso-atrial shunt if the IVC is involved).

13.9 Diseases of the gallbladder and pancreas

Gallstones

Pathophysiology Most gallstones are cholesterol gallstones. However, occasionally pigment gallstones are encountered. The latter are usually seen in the setting of a chronic hemolytic anemia with bilirubin, calcium and heme as the 'core' of the stones.

Cholesterol gallstones tend to form whenever bile is supersaturated with cholesterol and its composition falls outside the metastable region in the triangular plot of bile acids, cholesterol and lecithin concentrations (Fig 13.1).

Epidemiology There are important regional differences in India in the prevalence of gallstones. There is a high prevalence in north India (specially Rajasthan, Jammu and Kashmir, UP and Bihar) while it is less common in south India.

Natural history The majority of gallstones are silent for a variable period after formation. Upto 50 per cent of subjects with gallstones, however, are likely to develop symptoms over the next five years (Fig 13.17). Occasionally the initial presentation may be with a serious illness like cholangitis or pancreatitis, or with surgical obstructive jaundice. More often, gallstones may cause episodes of biliary colic or cholecystitis. They rarely, if ever, cause flatulence or dyspeptic symptoms though formerly such symptoms were often attributed to gallstones.

Biliary Colic

This term is a misnomer as the pain caused by gallstones is hardly ever waxing and waning (as in the classic colic). It is a constant severe pain located in the epigastrium or right hypochondrium, and is so severe that the patient tosses about and cannot lie still. It is accompained by nausea and often vomiting as well. The pain frequently lasts for 3–4 hours, radiates to the interscapular region. It often occurs early in the morning as in the supine position the gallstones may obstruct the cystic duct. Clinical examination may reveal tenderness in the right hypochondrium: this is known as *Murphy's sign.*

Acute Cholecystitis

The three inciting factors for an episode of cholecystitis are stasis, bacterial infection and ischemia, in that order of importance. Most episodes of acute cholecystitis are related to gallstone-provoked cystic duct obstruction with consequent bile stasis. Bile stasis initiates inflammation of the wall of the gallbladder due to the high concentration of lysolecithin and bile salts which provoke inflammation. The stasis is exacerbated further due to profuse secretion of fluid by the mucosa of the inflamed gallbladder.

Investigations The clinical picture and demonstration of the gallstones on ultrasound strongly suggests the diagnosis. Biliary scintigraphy with Technetium-labelled

iminodiacetic acid derivatives (HIDA, PIPIDA) injected intravenously reveals a patent bile duct but the gallbladder is not visualised. This test is reasonably specific.

Management The three factors which guide the treatment include the severity of cholecystitis, the general condition of the patient, and the firmness of the diagnosis itself.

Supportive care is vital and is aimed at correcting fluid and electrolyte imbalances by intravenous fluids. Intravenous administration of antibiotics (ampicillin or acephalasporin) is usually indicated in acute severe cholecystitis. A combination of antibiotics is preferred in patients with evidence of gram-negative sepsis or in diabetics. Surgical treatment can be either an immediate/early cholecystectomy (18–72 hours) or a delayed/interval cholecystectomy (6–8 weeks). The advantages of an early operation include a decrease in total morbidity and mortality and a reduction in cost as compared to expectant therapy. Surgery may be delayed if the patient is high risk or the diagnosis is in doubt.

Prognosis The overall mortality is five per cent. The adverse prognostic factors include old age (>70 years), diabetes mellitus, associated choledocholithiasis, associated pancreatitis or any supervening suppurative complication.

Choledocholithiasis (Common bile duct stones)

These are usually associated with gallbladder stones and the usual manifestations include:

1. obstructive jaundice,
2. cholangitis, that is, bacterial infection due to biliary stasis, and
3. provoking an attack of acute pancreatitis.

Surgical treatment is most often the preferred approach for treating symptomatic gallstones. Open cholecystectomy (for gallbladder stones) with choledocholithotomy (for bile duct stones) is one approach. Laparoscopic cholecystectomy is an attractive alternative; this minimal-access procedure is less expensive but as effective as the 'open' approach.

Medical dissolution of cholesterol gallstones has been attempted by feeding one of the primary bile acids — chenodeoxycholic acid. The dissolution rate is however only 50 per cent after two years of treatment; half the patients in whom stones dissolved initially will have recurrent stones over a period of five years. The other modes of treatment undergoing clinical trials include direct percutaneous injection of solvents into the gallbladder and fragmentation of the stones by shock waves (lithotripsy).

Pancreatitis

Pancreatitis refers to any inflammatory disorder of the pancreas. It may be classified as *acute, chronic* or *chronic relapsing.* In chronic relapsing pancreatitis, acute attacks are superimposed on a gradually deteriorating chronic pancreatitis.

Acute pancreatitis

Etiology The disorders commonly associated with acute pancreatitis are alcohol abuse, gallstones blocking the sphincter of Oddi through which the pancreatic secretions enter the duodenum, abdominal trauma including that due to surgery, viral infections (mumps, hepatitis, Coxsackie), drugs such as steroids, thiazide diuretics, INH, and hypertriglyceridemia.

Pathogenesis The pancreas is normally protected from autodigestion by three mechanisms.

1. The enzymes are 'packaged' as inactive precursors (called *zymogens*) within secretory granules. They are activated only within the duodenum by the activator enzyme enterokinase.
2. There are *protease inhibitors* within the pancreatic cell, in the secretions and in the plasma.
3. *Feedback inhibition*: As trypsin enters the duodenum, it breaks down cholecystokinin into smaller peptides which inhibit further secretion of trypsin.

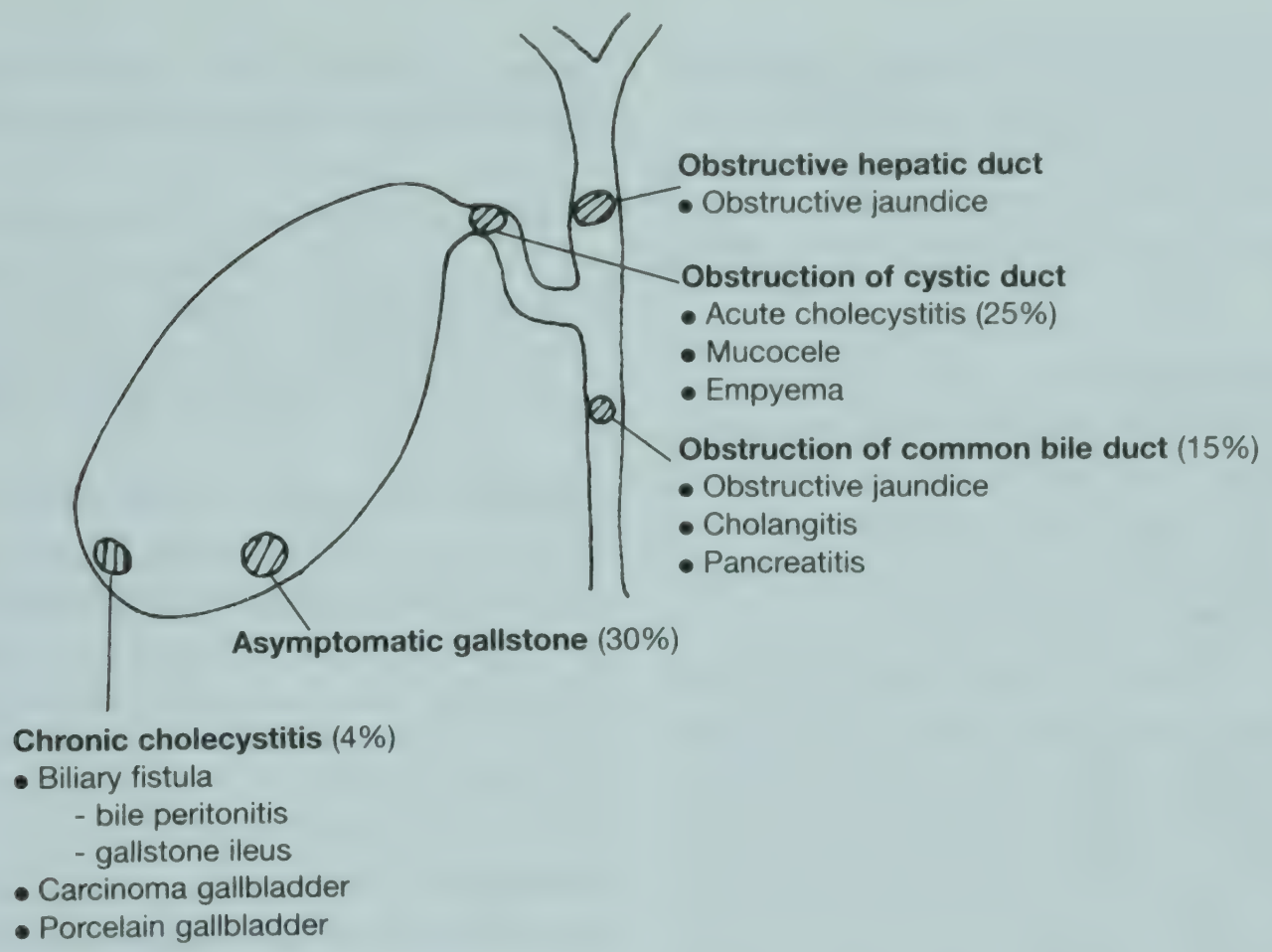


Fig 13.17 Possible complications in the natural history of gallstone disease

In pancreatitis, the enzymes are activated within the pancreas itself, following fusion of the secretory granules with lysosomes within the cell. Obstruction of the pancreatic duct worsens but cannot in itself initiate this process.

Pathology The pancreas shows edema and swelling which is initially diffuse. The inflammation may subside at this stage or may localise in some area (*phlegmon*). This area may undergo sterile necrosis to form a *pseudocyst* or may become infected and form an *abscess.* In severe pancreatitis there may be multiple areas of necrosis and hemorrhage (*hemorrhagic pancreatitis*).

Clinical features The illness develops rapidly over less than 24–48 hours. Ninety per cent of patients recover, usually within one week. Ten per cent of patients die despite therapy.

The abdominal pain may be mild or very severe. It is epigastric or periumbilical in location with radiation to the back, chest and flanks. It worsens when the patient lies flat. The patient prefers to remain seated with her trunk flexed and her knees drawn up.

Complications These may be local or systemic.

Local

1. Pancreatic phlegmon, abscess, pseudocyst (should be suspected whenever signs and symptoms of pancreatitis persist for more than two weeks).
2. Invasion of adjacent organs resulting in intraperitoneal hemorrhage, bowel infarction or portal vein thrombosis.

Systemic

1. Cardiovascular: *shock,* pericardial effusion
2. Lung: pleural effusion, *ARDS* (adult respiratory distress syndrome)
3. Renal failure
4. DIC (disseminated intravascular coagulation)
5. Metabolic: a) hyperglycemia (due to increase in circulating glucagon, epinephrine and steroids, alongwith decreased insulin levels), b) hypocalcemia (calcium reacts

with fatty acids released during fat necrosis to form 'soaps' which are precipitated)
6. Encephalopathy
7. *Purtscher's retinopathy* (sudden onset blindness due to occlusion of the retinal artery)

Laboratory investigations These include tests undertaken to establish the diagnosis, incidental findings (which should not be taken as indicating another pathology) and tests to assess severity and to look for complications (prognostic tests).

Diagnostic: 1. *Serum amylase* levels are more than three times the normal. However, amylase is also released from the salivary glands, intestines, kidneys and from many cancers. The serum amylase levels may be elevated in pregnancy, alcohol intoxication, diabetic ketoacidosis, head injury, burns and after morphine administration. Hence, total serum amylase is not a specific test. Also the levels return to normal in 2–3 days. Serum amylase has two isoforms. 'P' isoamylase comes only from the pancreas. All other organs secrete the 'S' isoamylase. So elevated 'P' isoamylase levels are specific.

2. Serum lipase (elevated for 1–2 weeks)
3. Amylase estimation in pleural and peritoneal fluids.

Diagnostic and prognostic: *Ultrasound* and *CT scan* of the abdomen, where available, have replaced plain X-rays of the abdomen. Both ultrasound and CT can show the extent of pancreatic inflammation and indicate whether there is any gallstone, and any complication such as a pancreatic pseudocyst or an abscess. Plain X-ray of the abdomen shows ascites and distension of bowel loops. Its chief value lies in excluding intestinal perforation (the latter would show air under the diaphragm in an erect abdominal X-ray film).

Incidental abnormal findings These include leukocytosis (15,000–20,000/μl), and ECG changes showing ST-T wave abnormalities similar to those seen in myocardial ischemia.

Prognostic indicators Factors associated with a poor prognosis are hyperglycemia, hypocalcemia, hyperbilirubinemia (and raised hepatic enzymes), hypoalbuminemia, hypoxemia, hypertriglyceridemia and hemorrhagic ascites.

Differential diagnosis The other causes of an 'acute abdomen' syndrome (such as perforated peptic ulcer, intestinal perforation, cholecystitis and renal colic), diabetic ketoacidosis, myocardial infarction and polyarteritis nodosa should be considered in the differential diagnosis.

Treatment The underlying principle of treatment is to reduce pancreatic secretion (and hence autodigestion) until the normal protective mechanisms outlined earlier, become active once more.

One can 'rest the pancreas' by stopping oral intake and by continuous nasogastric suction through a Ryle's tube to keep acid from entering the duodenum. Anticholinergics, histamine (H-2) antagonists (cimetidine, ranitidine) and glucagon have not shown efficacy in clinical trials.

Fluids (including colloids) are essential to correct volume deficits and to prevent circulatory shock. Replacing of calcium and giving insulin to decrease hyperglycemia are other adjunctive measures which are sometimes required.

Fluid may be removed from a pseudocyst by CT-guided aspiration. In severe pancreatitis peritoneal lavage was advised earlier, but it is not sufficient. Instead, surgery to remove necrotic tissue and obstructing gallstones (by sphincterotomy) may be required.

A pancreatitic abscess requires antibiotics and surgery. Prophylactic antibiotics and enzyme inhibitors (aprotinin) have not proven useful.

Chronic pancreatitis

In patients with chronic pancreatitis, less than 10 per cent of pancreatic exocrine function remains.

Etiology The causes include alcoholism, severe malnutrition, cystic fibrosis, posttraumatic and idiopathic chronic pancreatitis.

Symptoms The patient may present with either abdominal pain, or steatorrhea, or with both. Abdominal pain is unresponsive to antacids and is worsened by heavy meals and by alcohol.

Diagnostic evaluation In chronic pancreatitis, serum amylase and lipase levels are not elevated; a classic 'triad' of pancreatic calcification on the X-ray, steatorrhea and diabetes mellitus is seen in a third of patients. Cholestatic jaundice may be present. The tests for malabsorption have been described earlier. Ultrasound, CT scan and ERCP (endoscopic retrograde cholangiopancreatogram) are useful investigations.

Treatment 1. Relief of pain: Patients should avoid alcohol and large, fatty meals. Narcotic analgesics may be required for relief of pain. Surgical attempts have included resection of a stricture in the pancreatic duct, side-to-side pancreatico-jejunostomy and pancreatic resection (wherein 50–90 per cent of the gland is removed). The last procedure is most effective but causes a 'brittle' diabetes mellitus.

2. Malabsorption: Pancreatic enzymes and antacids to keep the duodenal pH high have not proved useful. Oral or parenteral vitamin supplementation may help treat the vitamin deficiency resulting from malabsorption.

Complications In addition to complications like diabetes mellitus, malabsorption, effusions in the pleura, peritoneum or pericardium, gastrointestinal bleeding, gastric erosions, icterus, subcutaneous fat necrosis and bone pains, there may be a slightly increased risk of pancreatic carcinoma. Narcotic addiction is a potential problem in subjects with severe recurrent abdominal pain.

KEY CONCEPTS

Biliary calculi

- Biliary calculi may have *cholesterol* (supersaturation with cholesterol, accelerated nucleation, abnormal motility) or *pigment* (infections, chronic hemolytic states) as the major constituent or they may be of the *mixed* type. Biliary calculi may be found in the gallbladder (*cholelithiasis*) or in the common bile duct (*choledocholithiasis*).
- Biliary *colic* is the classic manifestation; features include epigastric/RUQ abdominal pain, nausea and vomiting. Other *complications* include cholangitis (*Charcot's biliary* triad: pain, fever with chills, jaundice), obstructive jaundice, acute and chronic cholecystitis, acute pancreatitis, gallstone ileus.
- Fifty per cent of pigment stones and 15% of cholesterol stones are radio-opaque. OCG was earlier used for evaluating gallstones; it has now been replaced by US (sonographic hallmark of a stone is *acoustic shadowing*).
- Treatment with cholecystectomy (with bile duct exploration when necessary) is contemplated if the symptoms are frequent and disabling or if there is a history of a prior complication (such as pancreatitis). In poor risk patients with CBD stones, endoscopic sphincterotomy may be considered. Alternative therapeutic modalities which have been evaluated include use of oral bile acids for dissolution, intrabiliary infusion of solvents and lithotripsy.

Acute cholecystitis

- It is usually precipitated by cystic duct obstruction by a stone. An *acalculous* variety is seen in patients with trauma, burns, vasculitis, diabetes mellitus, parasitic infestation of the biliary tract and in the post-operative state.
- The clinical features include fever, pain, nausea, vomiting, RUQ tenderness (*Murphy's sign*) and a palpable gallbladder (<50%); rebound abdominal tenderness suggests perforation.

- Laboratory tests reveal leucocytosis, increased amylase, and increased bilirubin; The US reveals biliary stones. Radionuclide cholescintigraphy is diagnostic: CBD is seen but the gallbladder is not.
- The *complications* include hydrops, empyema, perforation and GI fistula with ileus.
- Management consists of medical treatment (meperidine for pain, nil orally, nasogastric suction, i.v. fluids, antibiotics) and early definitive surgery.

Acute pancreatitis

- Gallstones and alcohol intake account for most cases; uncommon causes include drugs, hypertriglyceridemia and viral infections (mumps).
- The common substrate is pancreatic *autodigestion* due to intrapancreatic activation of proteolytic zymogens; histology is characterised by pancreatic edema, necrosis and hemorrhage.
- Clinical presentation is with severe midepigastric pain radiating to the back and which is often relieved by leaning forward. In *severe* cases, the following signs may be seen: abdominal distension, rigidity, Cullen's and Turner's signs, shock. The *complications* include ARDS, shock, phlegmon, abscess and pseudocyst.
- Increased amylase levels in serum (and urine) are suggestive of pancreatitis but are not specific. A plain abdominal X-ray film may show localised ileus LUQ (*sentinel loop*); it also serves to exclude perforation (differential diagnosis).
- The adverse *prognostic factors* include age above >55 years, TLC >16,000/mm^3, hyperglycemia >200 mg/dl, elevated LDH and SGOT (on admission); Ca <8 mg/dl, hypoxemia, falling hematocrit, increasing azotemia, fluid requirement >6 litres (at 48 hours).
- The ultrasound may reveal biliary or pancreatic calculi. CT is important for diagnosis and for assessing severity. If an epigastric lump is present, needle aspiration and bacteriologic examination are important for distinction between a pancreatic phlegmon, a pancreatic abscess and a pancreatic pseudocyst.
- The treatment for *mild to moderately severe attacks* consists of avoiding oral feeds, administration of i.v. fluids, instituting nasogastric suction for relieving any ileus, and adding antibiotics if there is evidence of infection. For severe attacks, the following additional measures are instituted: volume replacement (6–8 litres per day), monitoring P_aO_2 and correction of any associated hypocalcemia. Removal of an associated gallstone is important if it is the inciting factor.

Chronic pancreatitis

- CP may be related to chronic alcohol intake or to calcific pancreatitis (in tropics).
- Episodic abdominal pain is the most common presenting complaint. Steatorrhoea occurs when there is over 90% loss of pancreatic function; diabetes mellitus occurs still later.
- Serum amylase is usually normal. An X-ray of the abdomen may reveal pancreatic calcification (over the body of the second lumbar vertebra). The US shows pancreatic calculi and dilated pancreatic ducts. If obtained, the secretin test is abnormal. Alternatively, a normal d-xylose test but an abnormal bentiromide test is suggestive of pancreatic exocrine dysfunction.
- Management includes the treatment of pain with a 3–4 week trial of large doses of pancreatic enzyme extracts, analgesics, and by recommending abstinence from alcohol; steatorrhea responds poorly. Diabetes mellitus seldom requires any treatment, and ketoacidosis is rare.

13.10 Malignant tumours of the gastrointestinal and hepatobiliary system

Carcinoma of the Esophagus

Incidence Esophageal carcinoma is uncommon in the western hemisphere. A high incidence is seen in Asia, especially in pockets of north China and Iran. There is a male predominance and also a preferential affliction of African Americans.

Etiopathogenesis The predisposing conditions for esophageal cancer include dietary factors such as alcohol consumption and smoking, prior esophageal disease such as lye-induced strictures, achalasia cardia and the Barret esophagus, and hereditary influences such as the rare disease tylosis.[1]

Pathology Most esophageal carcinomas are squamous cell carcinomas. Adenocarcinomas may be found in the esophagogastric region.

Clinical features Progressive dysphagia for solids is the cardinal symptom. Regurgitation of food and progressive weight loss are common. Substernal pain follows dysphagia and indicates extension of the tumour beyond the wall of the esophagus. Invasion of the mediastinal structures results in hoarseness (recurrent laryngeal nerve involvement), tracheo-esophageal fistulae or esophagobronchial fistulae. Pulmonary complications (pneumonitis, abscess) result from aspiration of regurgitant fluids.

[1] Inherited disorder with thickened skin of palms and soles

Diagnosis A barium swallow and endoscopy-guided biopsy can establish the diagnosis in most cases. Computerised tomography of the thorax is useful in evaluating the presence and extent of nodal and extranodal spread.

Treatment and prognosis Radiotherapy is the treatment of choice for tumours in the upper third and proximal part of the middle third of the esophagus (total dose of 6000 rads). Surgery is confined to resectable disease of the lower third and distal mid-third of the esophagus. Surgical mortality is high (10–15 per cent) and overall five-year survival rates are only about five per cent.

Carcinoma of the Stomach

Incidence The incidence of gastric carcinoma shows considerable worldwide variation, being more in Japan, South America and eastern Europe. There is an inverse relationship between the incidence of carcinomas of the stomach and those of the colon in some populations. There is also a male predominance (M:F=2:1)

Etiopathogenesis Premalignant conditions of the stomach include atrophic gastritis, large (>2 cm) adenomatous polyps, pernicious anemia and a prior gastric resection for ulcer disease. There is an association with blood group A, lower socioeconomic status, vitamin C deficiency with the intake of a diet high in salted fish and nitrosamines. Patients with

immunodeficiency disorders, especially common variable immunodeficiency, can develop gastric malignancies.

Pathology Most malignant tumours of the stomach are adenocarcinomas which arise from the mucous cells and are most frequent in the distal third of the stomach. They may be exophytic, ulcerative or diffusely infiltrative (*linitis plastica* or *leather bottle* stomach). Several histologic types are described, of which the intestinal type (resembling colonic carcinoma) has a better prognosis.

Clinical features Almost all subjects with gastric cancer have anorexia and weight loss. Early satiety and anemia due to chronic occult blood loss are other common symptoms. Epigastric pain which may or may not mimic ulcer disease is seen in several patients. Certain symptoms may indicate the location of the tumour. Cancer of the cardia commonly presents with dysphagia whereas pyloric tumours can present with symptoms of pyloric obstruction and 'retention' type of vomiting. When physical examination reveals an epigastric mass, the tumour has usually spread and has become inoperable. Other physical findings include left supraclavicular lymph nodes *(Virchow's nodes)*, a mass in the 'prerectal' pouch *(Blumer's shelf)* or palpable ovarian masses *(Krukenberg tumours)* and ascites.

Diagnosis A double-contrast barium study has an accuracy of 90–95 per cent for early, small, superficial gastric tumours. The finding of a polypoid mass, an ulcer with an irregular base or within a mass, or erosion of mucosal folds with areas of rigidity and absent peristalsis all suggest gastric malignancy. When combined with endoscopy and biopsy the diagnostic accuracy approaches 100 per cent.

Staging to determine the extent of spread is carried out by ultrasonography, abdominal CT and liver function tests.

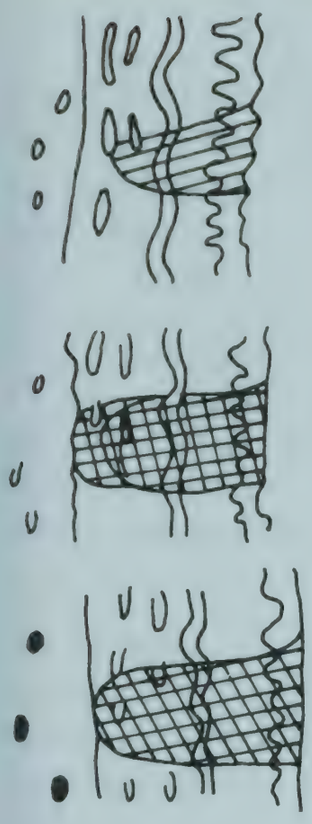
Treatment and prognosis If the tumour is localised, subtotal gastrectomy (for tumours of the distal stomach) or total gastrectomy (for proximal tumours) alongwith regional lymph node resection may be attempted. For metastatic disease, surgery is confined to palliative procedures for relief of gastric obstruction. Neither radiotherapy nor chemotherapy provide any significant survival benefit. The overall five-year survival is less than 10 per cent, though survival rates as high as 80 per cent have been noted in Japan following aggressive screening and resection of early superficial spreading cancer.

Carcinoma of the Colon

Incidence Colorectal cancer is one of the three commonest major internal malignancies in the developed countries the other two being lung cancer and breast carcinoma. It is more common in these countries as compared to the east or to countries in the African subcontinent.

Etiopathogenesis A high incidence of colonic cancer has been related to a diet rich in animal fat and low in fibre content. Prolonged colonic transit times with increased production of carcinogenic metabolites (due to the action of gut flora) is one of the postulated mechanisms. Inflammatory bowel disease and familial polyposis syndromes are also predisposing conditions. Whereas hyperplastic and juvenile polyps are not precancerous, 5 per cent of tubular adenomas and 40 per cent of villous adenomas undergo a malignant transformation.

Pathology and staging Adenocarcinoma is the predominant histologic type and prognosis is related to tumour staging (Fig 13.18). Roughly 55 per cent of colonic tumours are in the rectosigmoid and are therefore within reach of a sigmoidoscope. About six per cent occur in the descending colon, ten per cent each in the transverse colon and ascending colon. About 15 per cent of tumours have a cecal origin.



Duke's classification	*American Joint Committee on Cancer* staging	5 year survival
A (confined to bowel wall)	Stage 0 (in situ)	80–95%
	Stage I (Submucosa or muscularis propria involved)	
B (extends beyond bowel wall)	Stage II (Subserosa and beyond)	65%
C_1 (local nodes)	Stage III (nodes involved)	30–40%
C_2 (distant nodes)	Stage IV (metastatic disease)	10–20%

Fig 13.18 Staging of colonic tumours

Investigation Diagnostic studies include a meticulous physical examination including a digital rectal examination followed by proctosigmoidoscopy. If no lesion is evident but clinical symptomatology is suggestive, or if a fecal occult blood test is positive, a double-contrast barium enema can be performed. Any suspicious lesion on the barium enema is subjected to a colonoscopic biopsy.

Treatment For localised disease, surgical removal of the tumour (hemicolectomy for right- or left-sided tumours, and abdominoperineal resection for anal lesions) is the treatment of choice. Radiotherapy and chemotherapy are used for palliation of metastatic disease. Patients with resected lesions are followed up carefully with periodic colonoscopy. The carcino-embryonic antigen can be measured periodically, as a rise in serum levels often heralds tumour recurrence.

Prognosis The overall ten-year survival is 45 per cent; lesions confined to the mucosa have a ten-year survival rate of 80–95 per cent, those with invasion of the wall 60–80 per cent and those with metastasis confined to the regional lymph nodes have a survival of 40 per cent.

Carcinoma of the Pancreas

Incidence Carcinoma of the pancreas comprises more than 20 per cent of all gastrointestinal malignancies, being second in frequency after colorectal cancers. Middle-aged and elderly men are more often affected by this cancer.

Etiopathogenesis Though the exact cause of pancreatic carcinoma remains unknown, certain epidemiologic associations have been noticed. These include advanced age, chronic pancreatitis, diabetes mellitus, smoking, and a positive family history. There is an unconfirmed association with coffee consumption.

Pathology Most pancreatic carcinomas are adenocarcinomas arising from the ductal epithelial cells. Less than 10 per cent arise from the acinar cells. The latter are interestingly associated with subcutaneous fat necrosis producing palpable nodules, and with intra-medullary fat necrosis which results in bone pain.

Clinical features Abdominal pain is the cardinal feature and tends to be dull and boring, with some relief on bending forward. It may be localised to the epigastrium (in case of tumours of the head) or in the mid-abdomen or the left upper quadrant (in body and tail neoplasms). Weight loss and anorexia are frequent. Jaundice of an obstructive variety with a palpable gallbladder develops frequently in patients with malignancies of the head of the pancreas (in 80 per cent) but tends to be infrequent with lesions in the body or tail. Occasionally an epigastric mass may be palpable.

Uncommon symptoms include recent onset of diabetes mellitus, unexplained thrombophlebitis, upper gastrointestinal bleed (due to invasion of the duodenum) and, on occasion, depression.

Diagnosis Ultrasonography is usually the first imaging study followed by an abdominal CT for staging of the disease. An ultrasound or CT-guided aspiration may yield a cytologic diagnosis.

Treatment and prognosis Resectable tumours are treated surgically by the Whipple procedure for periampullary tumours, (that is, resection of pancreas with excision of the common bile duct and duodenum) or by total pancreatectomy with regional lymph node removal for lesions located elsewhere.

Palliative surgery may be considered for relief of biliary obstruction. Supravoltage radiation has also been used for palliation. The overall five-year survival is dismal (2–3%).

Hepatocellular Carcinoma

Incidence Whereas hepatocellular carcinoma is uncommon in the USA and Europe, it is one of the most common neoplasms in most of Africa and Asia. It is an important cause of mortality in middle-aged males in these regions.

Etiopathogenesis The important predisposing causes include underlying hepatic cirrhosis, (especially postnecrotic, alcoholic, or cirrhosis related to hemochromatosis) or α_1 antitrypsin deficiency. In southeast Asia, perinatal transmission of hepatitis B from infected mothers sets the milieu for later development of hepatocellular carcinoma; carcinogenesis is probably mediated by nuclear integration of the oncogenic antigen into the host genome. Dietary aflatoxins and androgenic steroids are other predisposing causes.

Pathology Microscopically, the tumours vary from being well-differentiated (resembling normal liver cells) to being anaplastic. An important variant is the *fibrolamellar variety* or polygonal cell carcinoma that occurs in younger adults, has an equal sex distribution, is not related to hepatitis B infection or cirrhosis and has a more favourable clinical course.

Clinical features Non-specific symptoms such as anorexia and weight loss are common. Hepatomegaly, and the presence of a hepatic bruit or of bloody ascites are more specific for the diagnosis. Clinical deterioration of an otherwise stable cirrhotic patient is an important indicator of the possible development of a hepatoma.

Diagnosis Ultrasonography is capable of identifying most liver tumours. Tumours usually have the appearance of hypoechoic lesions. Standard liver function tests are of little diagnostic help and serum α fetoprotein levels lack specificity. Selective hepatic arteriography may be required to determine tumour extent and operability. Ultrasound-guided aspiration may provide a cytologic diagnosis.

Treatment Hepatic resection can be attempted for solitary localised lesions in a non-cirrhotic liver. By and large all other therapeutic modalities have yielded disappointing results with an average survival of less than six months

Cancer of the Gallbladder

Etiology The most common predisposing condition for carcinoma of the gallbladder is cholelithiasis; yet, cancer supervenes in less than 1 per cent of patients with gallbladder stones followed-up over a ten-year period. The rare condition *porcelain gallbladder*[1] is also associated with a very high rate of malignant transformation.

Pathology and clinical features Carcinoma of the gallbladder affects women more often than men (4:1). It is a disease of the elderly (seventh decade). A majority of cancers are adenocarcinomas. Jaundice along with pain in the right upper quadrant of the abdomen are the most common presenting features. A mass may be palpable in the right hypochondrium.

Prognosis and treatment In the majority of patients, the cancer has become inoperable by the time the patient becomes symptomatic. Furthermore, the long term outcome is very bleak; one-year survival seldom exceeds 5 per cent. Although radiation and chemotherapy have been used, results have been uniformly disappointing.

Cholangiocarcinoma

Etiology Cancer of the hepatobiliary ductal system is often related to chronic parasitic infestations (Clonorchis infection Asia), sclerosing cholangitis,[2] and occupational exposure to chemicals (rubber industry). An association with gallstones has been described but is not as consistent as that seen with cancer of the gallbladder; gallstones are present only in about a third of patients.

Pathology and clinical features A majority of tumours are adenocarcinomas. The tumour may be focal, diffuse or nodular. Any stricture of the hepatobiliary ducts should be viewed with suspicion as it may be malignant. The eponym *Klatskin tumour* is used to describe tumours that originate at the junction of the hepatic ducts.

Cholangiocarcinomas present with painless jaundice, with or without a palpable gallbladder; the gallbladder is palpable when the tumour is distal to the cystic duct. Klatskin tumours and tumours of the cystic ducts are associated with a collapsed gallbladder. This malignancy has a slight male predilection (M:F=1.5:1). Patients are commonly in the fifth to seventh decade of life.

Prognosis and treatment Cholangiocarcinomas are associated with poor prognosis. The treatment is generally palliative and consists of surgical procedures to ensure adequate biliary drainage and relieve the obstructive jaundice.

[1] A condition characterised by calcium deposition within the wall of a chronically inflamed gallbladder

[2] A condition characterised by sclerosis and obliteration of the extrahepatic and intrahepatic bile ducts, usually occurring in association with inflammatory bowel disease

KEY CONCEPTS

Esophagus

- ➢ This is cancer usually of the squamous cell type, and the middle third of the esophagus is the most common site. Squamous cell cancer has been associated with alcohol intake, tobacco use, achalasia and tylosis. Adenocarcinoma is associated with Barrett's esophagus.
- ➢ The presentation is with progressive dysphagia and weight loss. Infiltration of the mediastinal structures can result in pulmonary aspiration, SVC obstruction or laryngeal paralysis.
- ➢ A barium swallow or an endoscopy with biopsy/brushings are diagnostic.

➢ Localised proximal lesions can be excised. Adenocarcinomas require surgery. Radiation is preferred for non-localised proximal tumours.

Stomach

➢ Gastric cancer is associated with dietary nitrates, chronic atrophic gastritis and polyposis. *Helicobacter pylori* has now been identified as a carcinogen (WHO). A higher incidence is seen in men.

➢ 95 per cent of gastric cancers are adenocarcinomas and over half of these originate in the distal stomach. Most gastric cancers are polypoid or ulcerating. Occasionally, they may be of the *superficial spreading* type or may result in a leather bottle stomach (*linitis plastica*).

➢ The symptoms include early satiety, epigastric pain and hematemesis. Pyloric tumours can cause obstruction while cardiac tumours can present with dysphagia. Gastric cancer is often metastatic at the time of initial clinical presentation; common metastatic sites include the liver, the peritoneum, the ovaries and the supraclavicular nodes.

➢ The diagnosis is by endoscopy with biopsy/brushings. Surgery may be curative for localised lesions. Palliative radiation may be offered to patients with metastatic disease.

Colon

➢ This is the most common GI neoplasm. Colonic cancer is associated with chronic inflammatory bowel disease, familial polyposis and a low fibre diet.

➢ 95 per cent of colonic cancers are adenocarcinomas. Colonic cancers tend to spread through the intestinal wall and serosa to the mesenteric nodes (Duke's staging). Left-sided colonic tumours are more common than right-sided ones.

➢ Ascending colonic tumours present with iron deficiency anemia. Descending colonic tumours may present with constipation, altered bowel habits or even a change in stool calibre. Rectal tumours may cause hematochezia.

➢ The diagnosis is by sigmoidoscopic or colonoscopic biopsy.

➢ Management consists of surgical excision followed by periodic colonoscopic surveillance for localised leisons. Postoperative radiation and chemotherapy may be beneficial. Chemotherapy with 5-FU (with folinic acid) is used for palliation of advanced tumours.

Liver

➢ *Secondaries* to the liver are more common than *primaries*. Primary tumours (hepatoma) are associated with postnecrotic cirrhosis, aflatoxicosis, hemochromatosis and chronic hepatitis B carriage.

➢ Presentations include: weight loss, RUQ pain, sudden deterioration in liver function in a cirrhotic. *Presence of an arterial bruit or a friction rub* over the surface of the liver is a suggestive finding.

➢ α-fetoprotein levels may be elevated. *Unusual associations* include hypoglycemia, erythrocytosis, hyperlipidemia and porphyria cutanea tarda.

➢ A biopsy is definitive. Usually hepatomas are non-resectable and have a poor prognosis. The *fibrolamellar variant* has a better prognosis.

Gallbladder

➢ Cancer of the gallbladder occurs principally in elderly women. It is almost always associated with gallstone disease.

➢ The clinical features include obstructive jaundice with an RUQ mass.

➢ The diagnosis is by ultrasound and CT.

➢ Usually the tumour is metastatic at the time of clinical presentation.

Pancreas

➢ Pancreatic cancer is more common in men and is associated with chronic pancreatitis, diabetes mellitus, and smoking.

➢ About 75 per cent of pancreatic cancers are adenocarcinomas; 75 per cent of pancreatic cancers occur in the head of the pancreas, and 75 per cent are metastatic at the time of initial presentation.

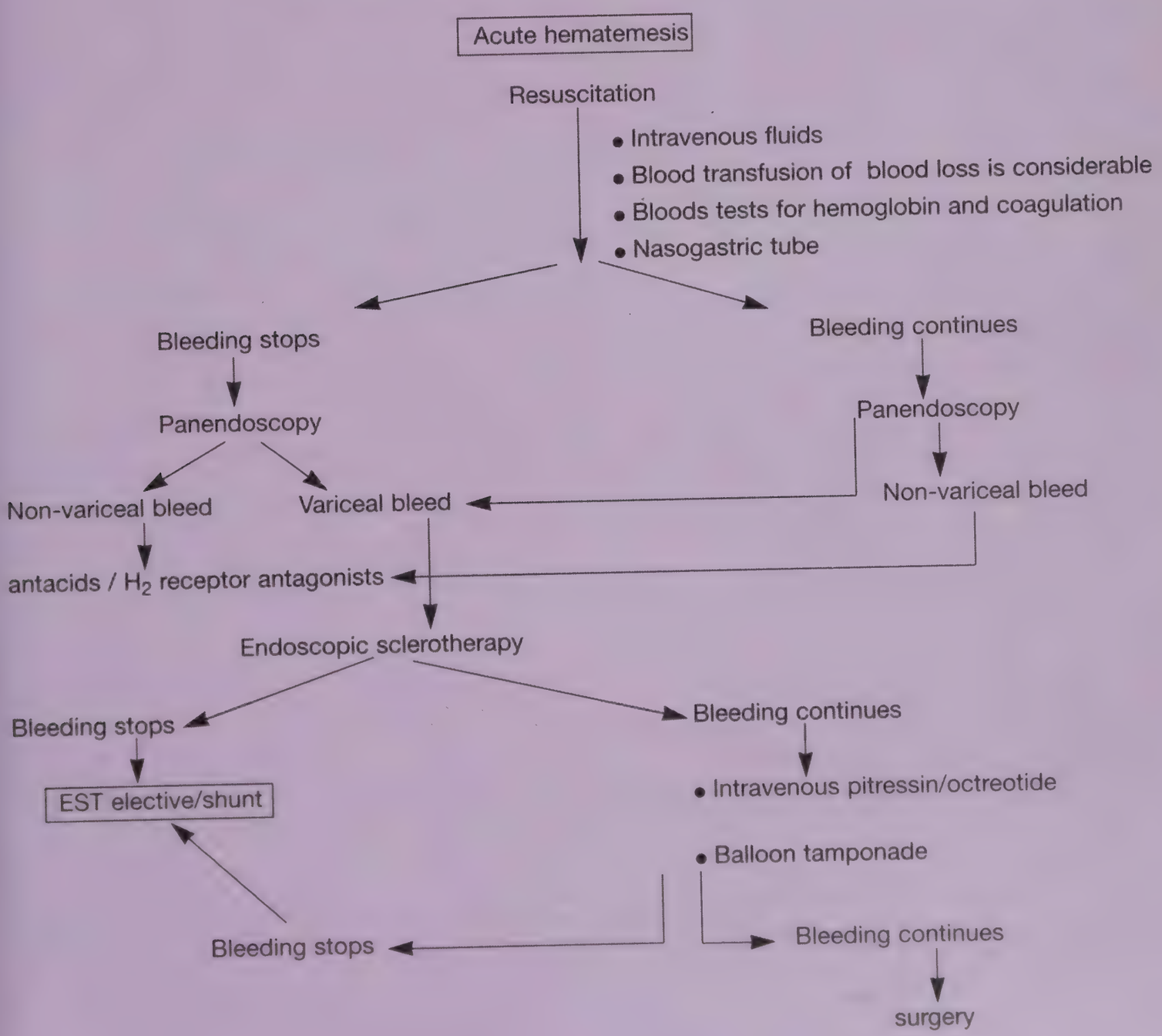
➢ The presentation is with surgical obstructive jaundice along with deep boring epigastric pain radiating to the back. Unusual manifestations include migratory thrombophlebitis; tumours of the body and tail of the pancreas can present with splenic vein obstruction.

➢ US or CT-guided needle aspiration yields tissue diagnosis.

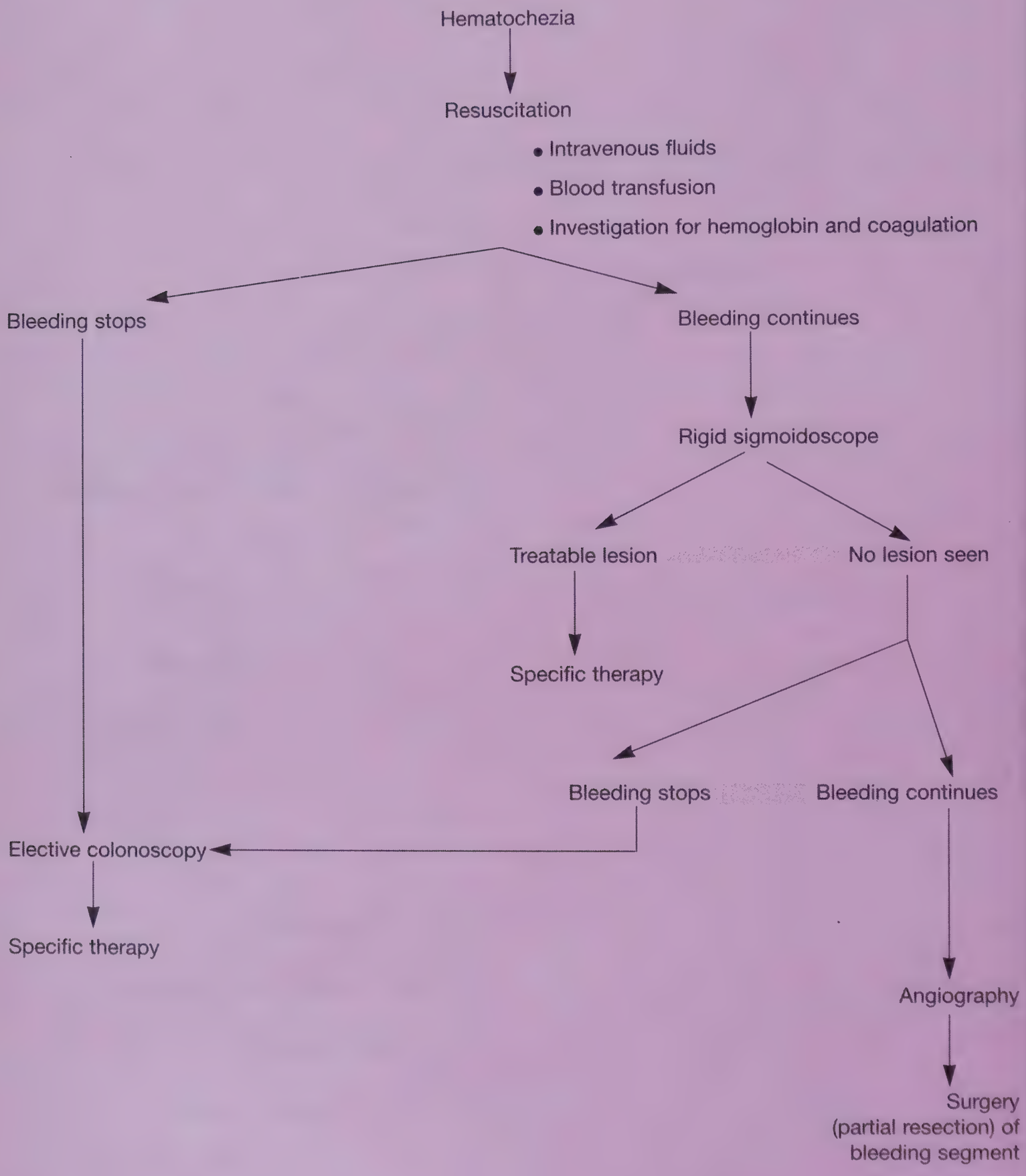
➢ Localised pancreatic tumours can be treated with Whipple's procedure. Non-operable disease may require stent placement to relieve obstruction, along with 5-FU for palliation.

13.11 Gastrointestinal emergencies

1. Management of upper gastrointestinal bleeding



2. Management of lower gastrointestinal bleeding



3. Management of fulminant hepatic failure

Fulminant hepatic failure

Clinical assessment

- Monitor fluid intake, output
- Investigate Hb, BUN, Na/K, ABG, TLC, prothrombin time
- Stool, sputum, blood, peritoneal fluid cultures
- Investigate likely etiology/precipitating event

Specific measures

- Vit K/ Fresh frozen plasma if coagulopathy
- Anticerebral edema measures (intravenous mannitol)
- Antibiotics if infection is present
- H_2 blockers to prevent gastrointestinal bleed
- Oral lactulose
- Avoid sedatives

Supportive measures

- Maintain caloric intake
- Avoid hypoglycemia
- Correct dyselectrolytemia
- Correct acid-base disturbances

* Liver transplantation has been used successfully in the U.S.A. for treating fulminant hepatitis which is non-responsive to conservative management. Charcoal perfusion has also been tried with limited success.

14

Renal Diseases

14.1 Basic renal physiology

The kidneys play a vital role in the constancy of the *milieu interior* of the body, that is, they maintain the composition, the volume and the tonicity of the extracellular and intracellular fluid compartments within a narrow physiologic range.

The Kidney

Each adult kidney lies retroperitoneally along one side of the vertebral column from vertebrae T12 to L3, weighs about 150 grams and measures 12 x 6 x 3 cm. It consists of an outer cortex and an inner medulla, the latter being formed by the renal pyramids. Each renal artery divides into five *segmental* arteries which further divide into *interlobar* arteries. The latter vessels divide at the corticomedullary junction into *arcuate* arteries. These arteries give rise to the interlobular arteries which in turn give rise to the afferent arterioles. The glomerulus is a fine capillary bed which is supplied by a single afferent arteriole and is drained by a single efferent arteriole. The venous drainage mirrors the arterial drainage.

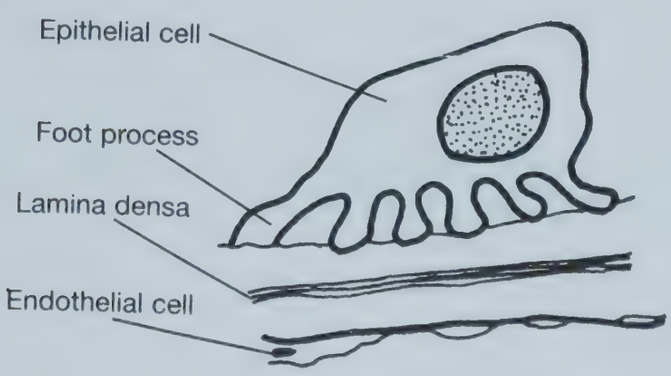


Fig 14.1 Podocyte

The functional unit of the kidney is the *nephron.* There are about a million nephrons in each kidney. Each nephron has a *malpighian corpuscle* and its attached tubule. The malpighian corpuscle is composed of the tuft of capillaries described as the *glomerulus* and the *Bowman's capsule,* an extension of the proximal convoluted tubule into which the glomerulus invaginates. The glomeruli are located in the renal cortex while the tubules are located in the medulla. The collecting ducts drain into the renal pyramids. The capillary wall in the glomerulus has three structures that compose the *filtration barrier.* The endothelial cells lining the lumen have pores of about 700Å between them. The basement membrane of the capillaries with a central *lamina densa* is about 200Å thick. The epithelial cells or the *podocytes* are the largest, and the gap between the foot processes is about 300Å (Fig 14.1). The *podocytes* are lined by a negatively charged glycoprotein known as the *glomerular polyanion* (anionic due to sialic acid). Abnormalities of the filtration barrier may occur in any of the three components, that is, swelling of the endothelial cells with obliteration of fenestrae (as in preeclampsia, acute post-

streptococcal glomerulonephritis), thickening of the basement membrane (as in immune complex disease) or fusion of the foot processes (which both cause and is a result of proteinuria in several forms of glomerulonephritis). Between the capillary tufts is the *mesangial matrix* composed of fibrillary mucopolysaccharides. Mesangial cells include modified smooth muscle cells and other phagocytic cells (dendritic cells). These dendritic cells express MHC Class II antigens on their surface (see Chapter 17) and serve as antigen presenting cells. The mesangial complex is an important site for the deposition of immune complexes. The renal tubule is composed of a proximal convoluted tubule, the pars recta (straight part), the loop of Henle, the distal convoluted tubule and the cortical collecting duct. These segments differ in the characteristics of their epithelium, the number and size of mitochondria, and the complexity of the brush border (microvilli). Where the cells of the distal convoluted tubule come into juxtaposition with the glomerular vascular pole, they become smaller and constitute the *macula densa*. The cells of the afferent arteriole in this region are granular and are called the juxtaglomerular cells. These two cell types form the JGA (*juxtaglomerular apparatus*) and the latter cells secrete renin (Fig 14.2).

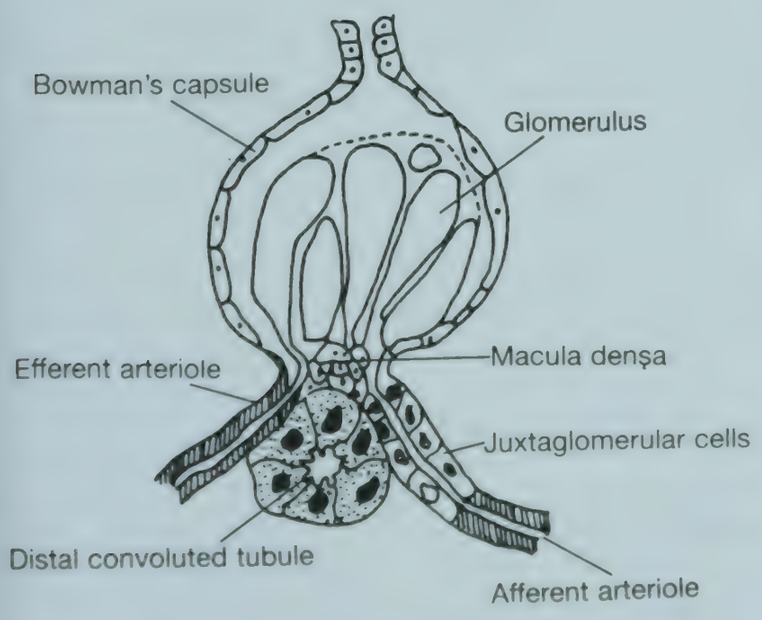


Fig 14.2 The juxtaglomerular apparatus

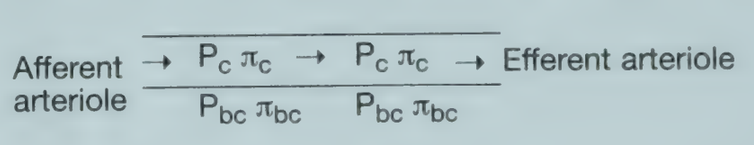
Normal Renal Function

Glomerular filtration

The formation of urine begins with ultrafiltration across the walls of the glomerular capillaries, a phenomenon which is an interplay of Starling's forces. Thus, the glomerular capillary hydrostatic force and Bowman's space oncotic pressure favour filtration whereas the glomerular capillary oncotic pressure and Bowman's space hydrostatic pressure oppose it. At the afferent arteriole the net forces favour filtration but as the glomerular capillary oncotic pressure increases (concentration due to ultrafiltration) and the hydrostatic pressure drops, the Starling forces in the peritubular capillaries are in the uptake mode (Fig 14.3). The larger juxtamedullary glomeruli have a filtration rate about double that of the superficial cortical ones (*single nephron glomerular filtration rate–SNGFR*). The filtration of molecules is governed by their size (*steric hindrance*) and their charges (electrostatic hindrance). Thus, molecules less than 10,000 daltons are freely filtered and so are positively charged molecules which are not repelled by the glomerular polyanion.

Tubular reabsorption

The ultrafiltrate across the glomerular capillaries is about 180 litres in a day. Yet, the urine volume is about 2 litres as 90 per cent



$GFR = K_f (P_c + \pi_{bc} - (P_{bc} + \pi_c))$

P_c, π_c = Capillary hydrostatic and oncotic pressure respectively

P_{bc}, π_{bc} = Hydrostatic and oncotic pressures in the Bowman's space

K_f = Permeability coefficient

GFR = Glomerular filtration rate

Fig 14.3 Starling's forces governing glomerular ultrafiltration

(178 litres) of the glomerular ultrafiltrate is reabsorbed by the renal tubules. Each division of the renal tubule has its own morphologic and physiologic distinctions. The proximal third of the proximal convoluted tubule reabsorbs 60–70 per cent of the filtrate, especially glucose, amino acids and organic acids. Bicarbonate reabsorption is also completed in this segment. The ultrafiltrate is isoosmotic with plasma and enters the straight portion of the proximal tubule, the pars recta, where organic acids (uric acid, penicillanic acid) are secreted. The loop of Henle reabsorbs more of sodium and chloride (25 per cent) than water (15 per cent) and hence the fluid entering the distal convoluted tubule is hypoosmotic to plasma. A remarkable mechanism called the *countercurrent* multiplier establishes the hypertonicity of the medullary interstitium and its physiologic basis is the differential permeability of the different segments of the loop of Henle to water and sodium chloride. Thus, the thin descending loop is highly impermeable to sodium but permeable to water, so that the isotonic urine becomes hypertonic. The thin ascending loop is impermeable to water but is highly permeable to sodium, so that the urine becomes hypotonic. The active reabsorption of sodium chloride by the thick ascending loop makes the urine even more hypotonic, simultaneously rendering the interstitium hyperosmolar. The latter would in turn increase the egress of water from the descending limb (Fig 14.4). Thus, the countercurrent flow in the two limbs of the tubule ensures a 'multiplier' effect, with maximum tonicity of urine at the tip of the loop. The distal convoluted tubule reabsorbs sodium (10 per cent) and secretes hydrogen ions, ammonia and potassium under the influence of aldosterone. The distal collecting duct regulates

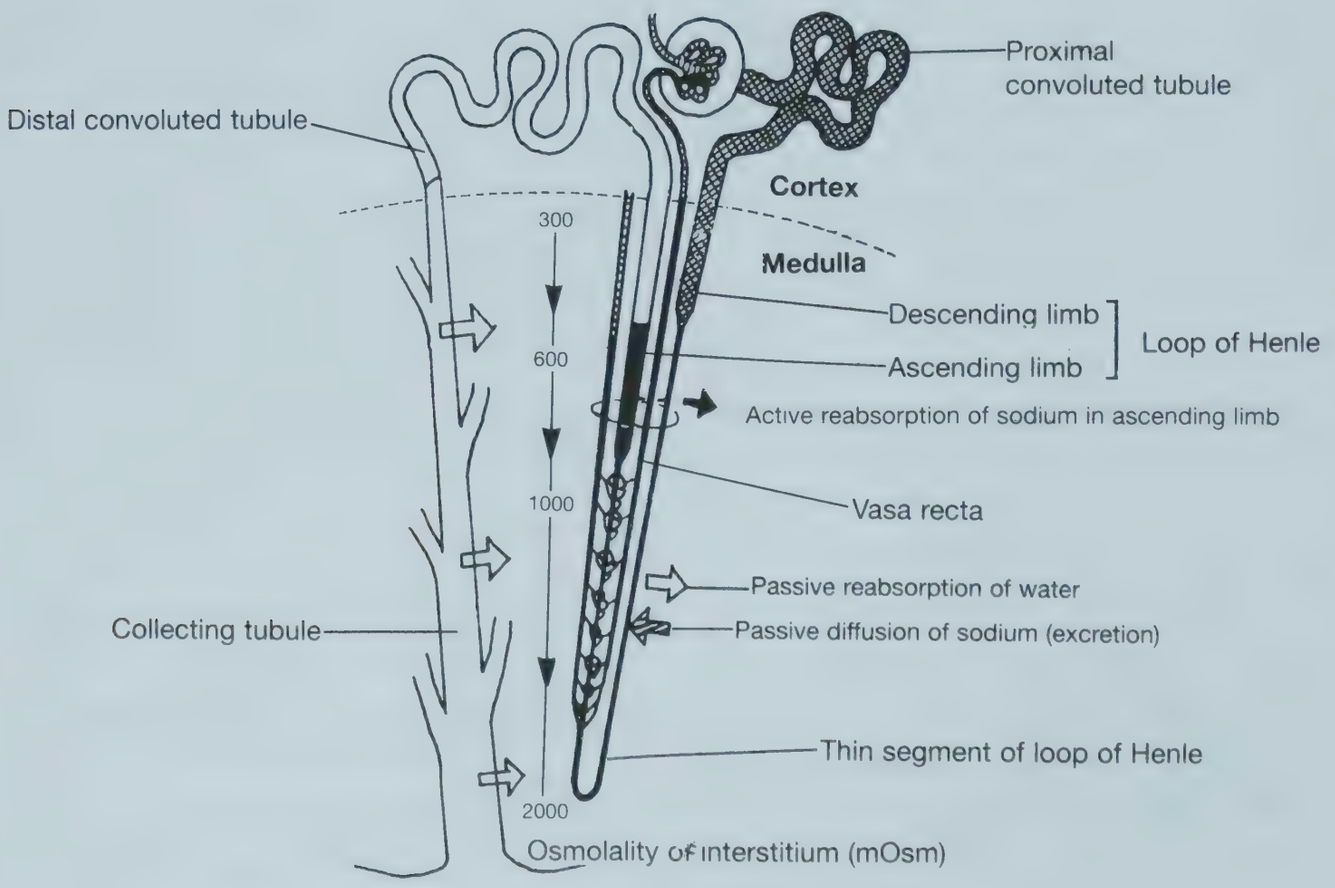


Fig 14.4 Tubular resorption

the osmolality of urine under the influence of the antidiuretic hormone. Thus, proximal tubular disorders are characterised by glycosuria, phosphaturia, aminoaciduria and bicarbonaturia, the latter resulting in acidosis (RTA II). Distal tubular disorders also result in acidosis (failure of secretions of ammonia), and have associated hypokalemia (RTA I). *Bartter syndrome* is suspected to be a disorder of the thick ascending limb of the loop of Henle. Its features are hyponatremia, hypokalemia, and compensatory hyper-reninemia. Nephrogenic diabetes insipidus is a disorder in which the collecting duct is refractory to the action of the antidiuretic hormone, resulting in polyuria.

Other functions of the kidney

Apart from being an excretory organ, the kidney is also an endocrine receptor as well as an endocrine organ. It serves as a receptor for the parathyroid hormone which increases calcium reabsorption and causes phosphaturia by increasing cellular AMP levels. The hormone also converts vitamin D_3 to its metabolically active form. The influence of aldosterone and ADH on the distal tubules and the collecting duct has already been referred to earlier. The kidneys synthesise *erythropoietin,* a glycoprotein stimulating hematopoiesis, and *renin* which converts angiotensinogen to angiotensin I (a decapeptide). The latter when converted to angiotensin II (octapeptide) is a potent vasoconstrictor, and a stimulus for thirst and aldosterone production. The kidneys also have a *kallikrein kinin* system and a *prostaglandin* system that regulate renal blood flow and sodium excretion.

14.2 Approach to a patient with renal disease

Approach to a Patient with Hematuria

Hematuria is defined as the presence of blood in the urine. This is a rather simplistic definition. The intern may encounter a patient who complains of passing 'red coloured urine'. This may be hematuria, but other possible causes like hemoglobinuria, porphyria and 'discoloured' urine (drugs like aminopyrine, aniline, phenolphthalein, phenazopyridine or infections such as *Serratia marcescens*– the 'red diaper' syndrome) can also exist. Microscopic hematuria is not overt and may be detected only on urine analysis. It is in no way different in prognosis from 'gross' hematuria.

Pathophysiology Hematuria occurs when red blood cells gain entrance to the urinary tract at any point ranging from the glomerular tufts down to the distal urethra. This abnormal 'leak' may be due to inflammation and consequent abnormal permeability of the glomerulus, pelvis, ureter or bladder, erosion of the mucosa by a stone, trauma or tumour or extravasation due to necrosis of parenchyma as in renal infarction or papillary necrosis. Normal urine contains red cells; their number ranges between 5×10^5 to 8×10^6 RBCs/litre which amounts to less than three red cells/high power field. When blood leaks from the lower urinary tract, hematuria tends to be 'gross'. Glomerular leakage of blood on the other hand tends to be 'microscopic'. The various causes of hematuria are depicted in Fig 14.5. Glomerular hematuria is associated with red cell casts in the urine. Gross hematuria occurs when the leakage of red cells is at least 5×10^6 RBCs/mm^3 of urine.

History Bleeding throughout the time of urination suggests a bladder lesion or an upper urinary tract source. Bleeding that occurs at the onset of urination (*initial hematuria*) suggests a bleeding source in the posterior urethra. *Terminal hematuria* suggests either the trigonal area of the bladder or the prostate as the source of bleeding (see *three glass test,* Fig 14.6). Stringy, worm-like clots (moulds of the ureter) indicate renal bleeding whereas large chunks of clots suggest bladder lesions. Painless and gross hematuria may suggest a kidney or bladder tumour and hematuria associated with ureteral or renal colic suggests nephrolithiasis. However, pain in the loins related to 'clot colic' may also occur with renal cell carcinoma, IgA nephropathy and the loin pain-hematuria syndrome.[1] Suprapubic pain associated with dysuria, frequency and urgency suggests cystitis but can also occur with a bladder calculus, invasive bladder neoplasm or tuberculosis of the bladder. A family history of hematuria may suggest inherited renal disease such as polycystic kidney disease, sickle cell anemia or benign familial hematuria. The patient's age may also suggest the etiology of hematuria; middle-age onset of hematuria suggests a urological neoplasm (100:1) and childhood onset suggests a glomerular cause. In a sexually active adult, prostatitis and 'honeymoon cystitis' are common

[1] A syndrome of obscure etiology seen in young women.

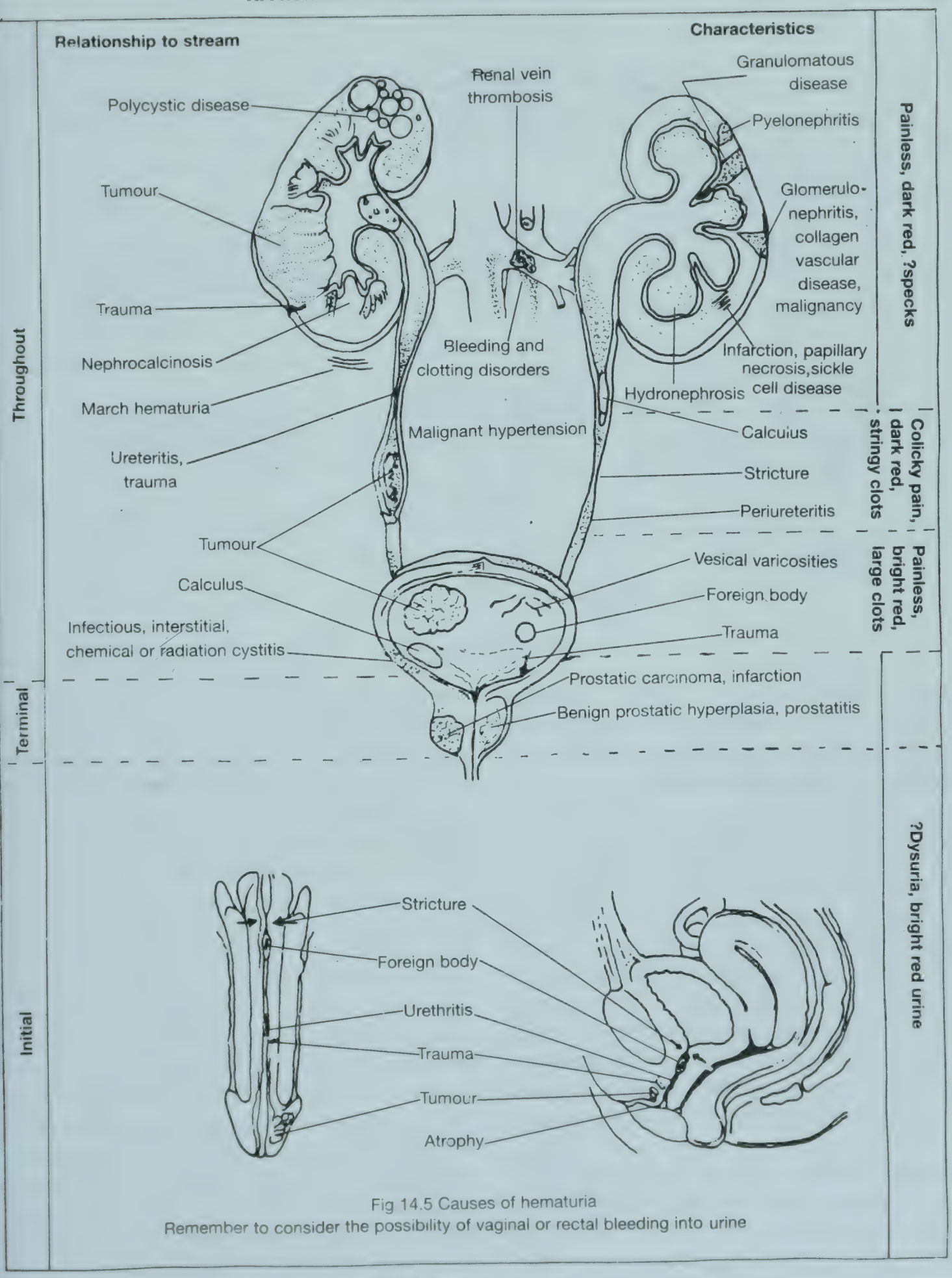


Fig 14.5 Causes of hematuria
Remember to consider the possibility of vaginal or rectal bleeding into urine

Fig 14.5 Causes of hematuria

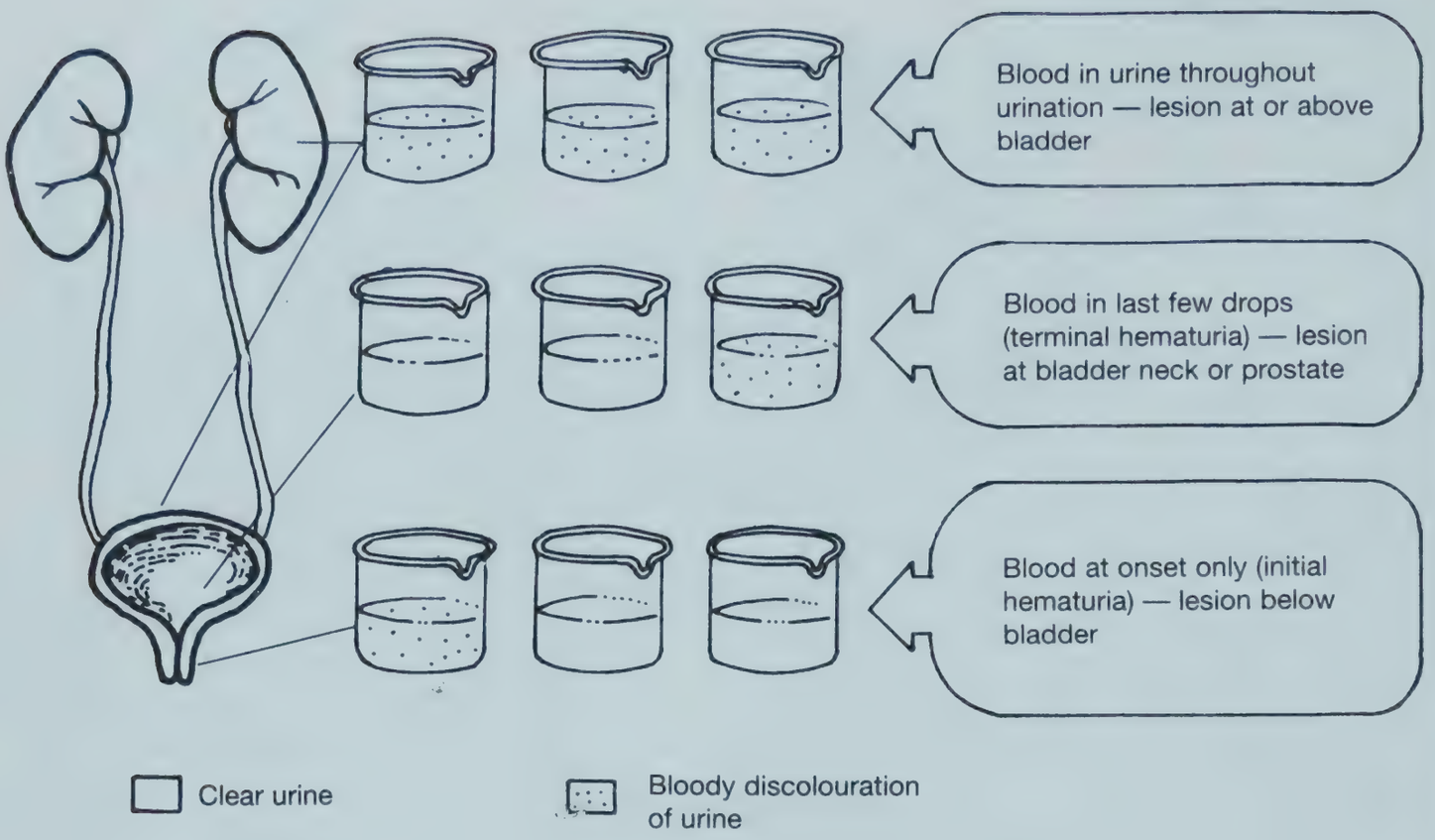


Fig 14.6 Three glass test

causes of hematuria. A history of bleeding tendencies may indicate a coagulopathy (Fig 14.7). A history of travel to an endemic zone may suggest vesical schistosomiasis.

Physical examination The presence of a 'mass' in the flanks suggests a 'polycystic' disease or a renal neoplasm. Costovertebral angle tenderness with fever indicates renal inflammation. Suprapubic tenderness suggests bladder inflammation and a tender prostate suggests prostatitis. Examination of the external genitalia will screen the other causes of hematuria such as a urethral 'caruncle' in a woman or carcinoma of penis in a man. Hypertension may suggest glomerulonephritis or polycystic kidney disease.

Laboratory studies *Dipstick* urinalysis uses a reagent strip impregnated with orthotoluidine and buffered organic peroxidase. Hemoglobin catalyses the oxidation reaction between these two substances, resulting in a predictable measurable colour, which is judged against a standard scale. Dipstick is more sensitive for hemoglobin than intact RBCs, recognising 0.3 mg hemoglobin/100 ml urine (the equivalent of 10 lysed RBCs/ml). Quantitative urinary microscopic analysis has shown that most normal individuals have <3 RBCs/hpf.

Isolated hematuria (without proteinuria) may have its source anywhere in the urinary tract. Small deformed cells indicate glomerulonephritis whereas 'larger red cells with normal appearance' suggest non-glomerular bleeding. *Phase contrast microscopy* can be used for identifying casts and an automated red cell counter can measure red cell size (urine red cell MCV <70 fl indicates glomerular bleeding; MCV >80 fl indicates non-glomerular hematuria). Hematuria associated with granular casts identifies glomerulonephritis as the cause whereas associated pyuria may indicate infection, calculus disease or tuberculosis. Macromolecular crystals in urine point to

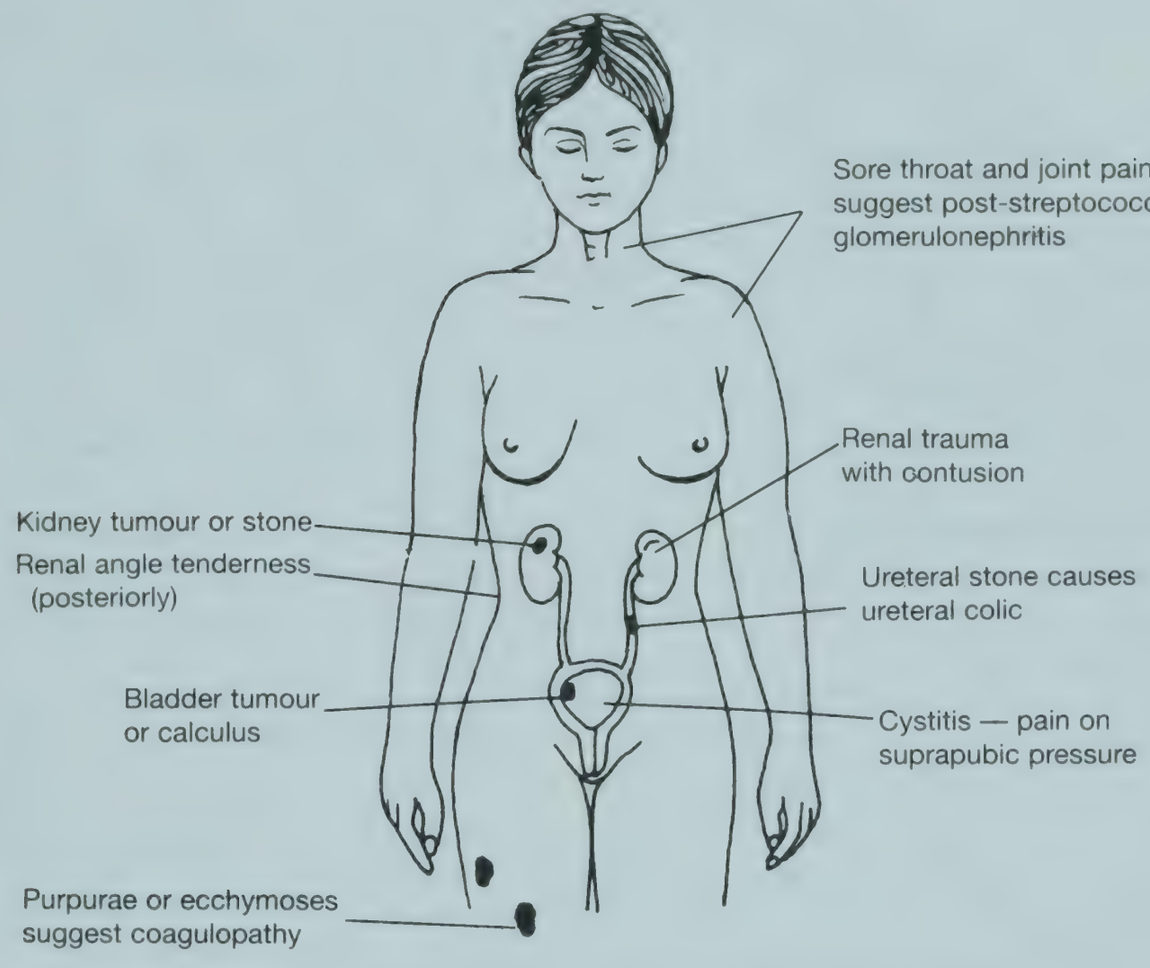


Fig 14.7 Causes of hematuria: history and examination findings

calculus disease. Hematuria with significant proteinuria (>500 mg/24 hours) is likely to be due to glomerular disease. *Alkaline pH* of urine with a positive result for nitrite and leukocyte esterase indicates urinary tract infection. Urinary examination for acid-fast bacilli can yield a positive result in urinary tract tuberculosis. First void *urinary cytology* can detect a malignancy in about two-thirds of the cases (10% of renal cancers and 70% of tumours of the bladder). A hemogram and coagulogram can identify sickle cell disease or coagulopathies.

Plain X-ray of the abdomen detects calcification. This may indicate in order of decreasing frequency calculus, tuberculosis, papillary necrosis or medullary sponge kidney. *Ultrasonography* can identify calculi, neoplasms and cysts, and guided fine-needle aspiration can be performed to get a tissue diagnosis.

Intravenous urography can outline space occupying lesions of the kidney and bladder. *Computerised tomography* is also of use in the diagnosis of renal neoplasms and their staging by identifying extracapsular spread and lymphadenopathy. If the IVU is normal, cytology is negative and a non-glomerular source of bleeding likely, *cystoscopy* and a guided biopsy may yield a diagnosis. *Retrograde pyelograpy* and ureteropelvoscopy have been utilised to identify filling defects in the ureter and pelvis.

A negative IVU and cytology and a likely glomerular source of bleeding can necessitate a renal biopsy (especially if associated with a nephritic presentation and deteriorating renal function) to rule out crescentic glomerulonephritis requiring immunosuppressive therapy. An algorithm for the evaluation of hematuria is given in Fig 14.8.

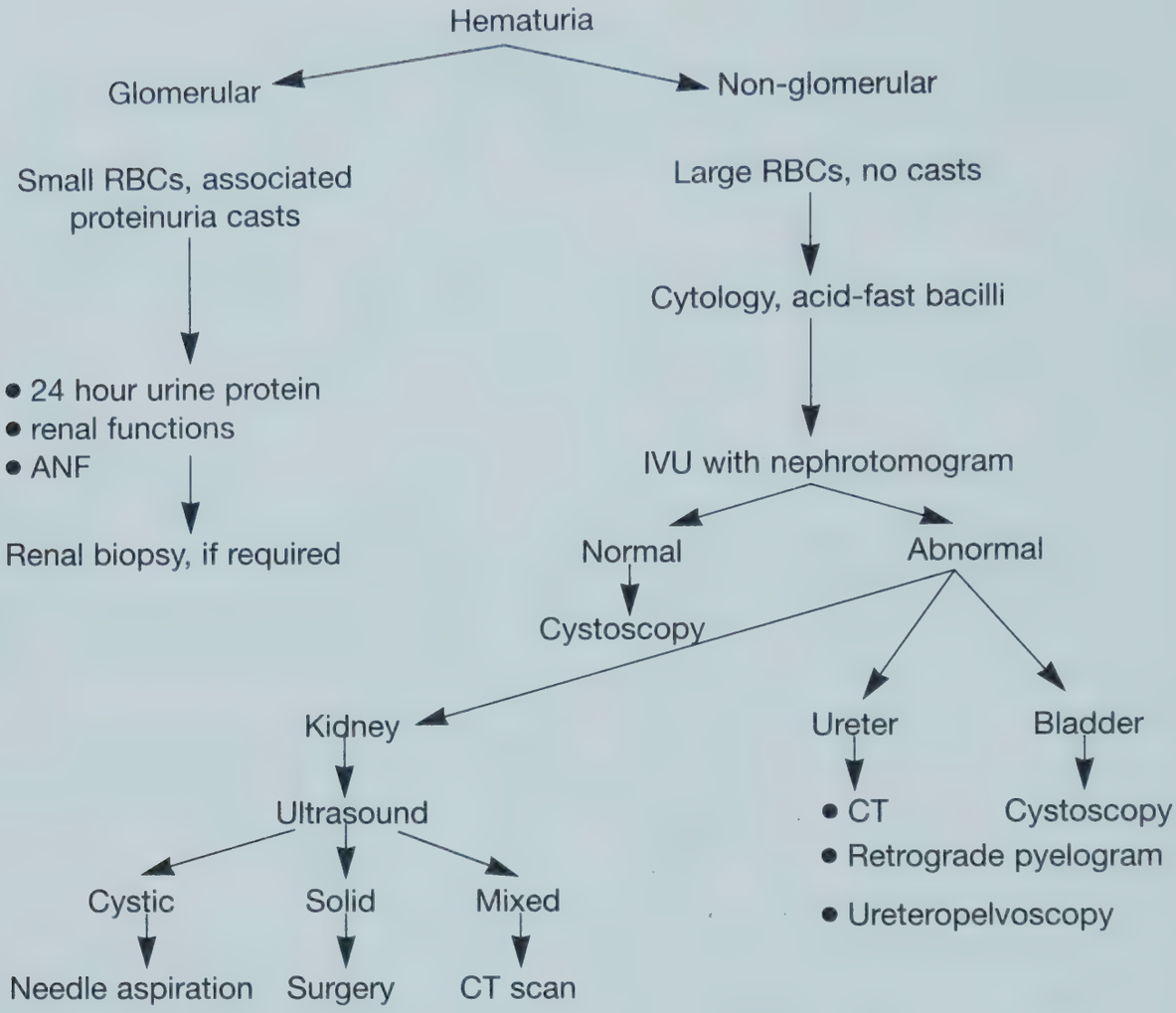


Fig 14.8 Algorithm for evaluation of hematuria

Approach to a Patient with Oliguria or Anuria

The renal solute burden of an average adult is 600 mOsm daily (varying with the muscle mass of the individual and the catabolic state of the body). Under the effect of maximum antidiuretic hormone secretion (and therefore maximum concentrating effect), the urine can be concentrated to an osmolality of 1200 mOsm/kg. Hence the minimum urine volume required to excrete the daily solute burden (600 mOsm) would be half a litre, which is the obligatory daily urine output. *Oliguria* is therefore defined as less than 500 ml of urine in 24 hours. *Anuria* is arbitrarily defined as urinary output of less than 100 ml in 24 hours.

Pathology The first concept to be appreciated is that in *chronic* glomerular diseases oliguria is uncommon (except in end stage renal disease with glomerular filtration rate less than 5.0 ml/minute). Even with a 75 per cent reduction in the glomerular filtration rate, the amount of water entering the tubules exceeds the urine volume by twenty times. Hence, if the renal tubules are functioning well and handling the solute burden normally, oliguria is unlikely in chronic renal failure. *Prerenal factors* such as hypovolemia (due to dehydration, bleeding, or 'third space sequestrations'[1] as in pancreatitis or peritonitis), cause renal hypoperfusion and hence a decline in urine output. In these conditions since the tubular function is normal, more than 99 per cent of the filtered sodium is reabsorbed; hence the fractional excretion of

[1] Third space sequestrations refers to the accumulation of fluid in a cavity or space such as the peritoneum or retroperitoneum.

sodium (FE_{Na}) is less than one per cent. The urine excreted is, therefore, low in sodium content (U_{Na} < 10 meq/L) and highly concentrated with a high osmolality (U_{Osm} > 500 mOsm/kg) due to a maximum antidiuretic hormone effect stimulated by hypovolemia. With normal tubules, the reabsorption of urea exceeds that of creatinine; the ratio of blood urea nitrogen/serum creatinine, therefore, increases to 15:1 or more (normally 10:1).

When oliguria is due to renal disease (classically represented by 'acute tubular necrosis') the dysfunctioning tubules fail to absorb sodium or urea and also fail to concentrate urine (Fig 14.9). Hence urinary sodium exceeds 20 meq/L, FE_{Na} exceeds one per cent (usually > 3 per cent), urinary osmolality declines (U_{Osm} < 350 mOsm/kg) and the ratio of blood urea nitrogen/serum creatinine remains in the normal range.

Postrenal causes (obstructive uropathy) are either characterised by total obstruction, in which anuria is likely, or by partial obstruction (Fig 14.10). The latter, being usually intermittent, is characterised by a fluctuating urine output. Renovascular causes of renal failure (renal artery embolism/occlusion) are also characterised by anuria.

History and physical evaluation The history should include a careful search for the cause of hypovolemia (dehydration, blood loss), and an enquiry into the use of potential nephrotoxic drugs. Diuretics and aminoglycoside antibiotics are the commonest offenders. Anuria should prompt one to look for clues of renal vascular occlusion such as a bruit, or an obstructive uropathy (for example palpable kidney or bladder). A physical examination must also be used to assess the state of hydration. The findings of diminished skin turgor, orthostatic hypotension and tachycardia support the diagnosis of hypovolemia and possible prerenal azotemia. The findings of edema, distended neck veins and circulatory congestion suggest decreased 'effective' renal blood flow as the cause.

Laboratory investigations A serum creatinine level above 2.5 mg/100 ml strongly suggests renal disease rather than prerenal azotemia. Urinary indices (U_{Na}, FE_{Na}, U_{Osm}) may help differentiate prerenal from renal causes as

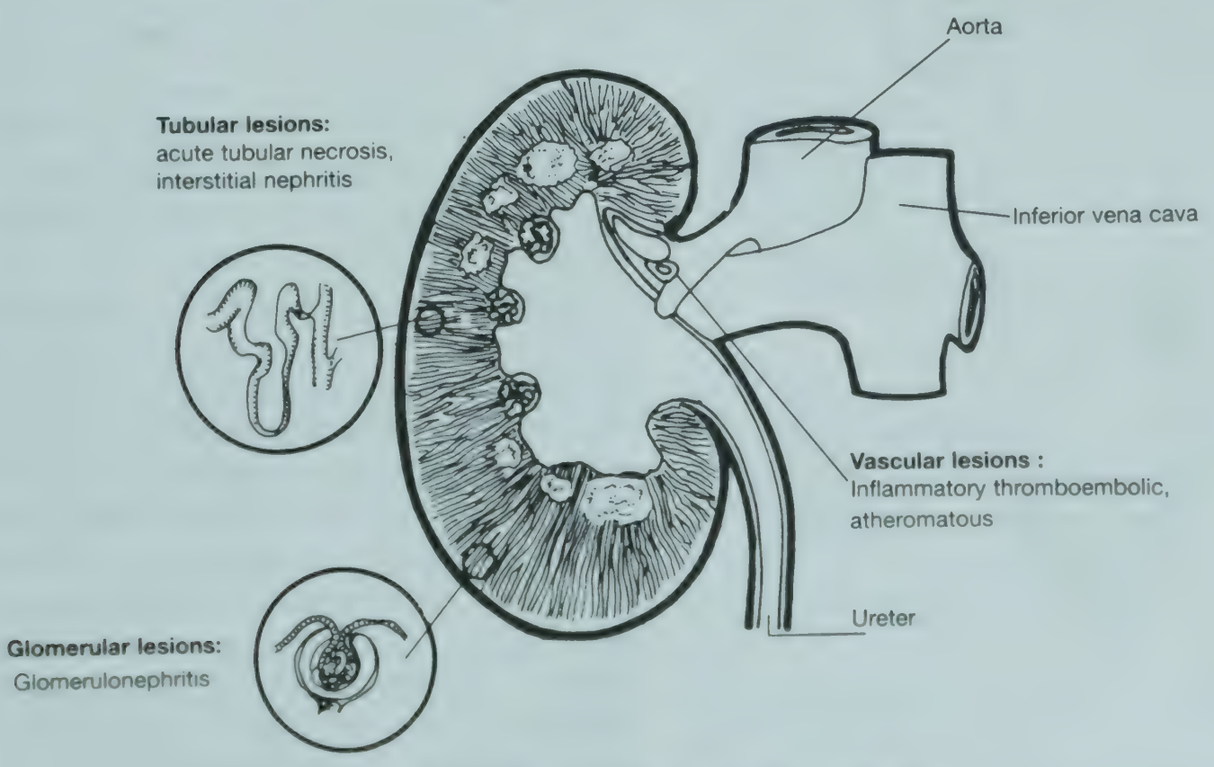


Fig 14.9 Renal parenchymal causes of oliguria

discussed in an earlier section. When the picture is not clear, a fluid challenge of one litre normal saline over an hour may be tried, provided there is no preexisting fluid overload. A response in the form of diuresis favours the diagnosis of prerenal azotemia. Anuria necessitates establishing the patency of the renal vessels (through radionuclide scanning) and of the excretory system (with ultrasound) before considering a renal parenchymal cause of anuria, such as acute cortical necrosis.

Approach to a Patient with Nocturia

The normal nocturnal urine production does not exceed bladder capacity. However, conditions associated with increased urine formation during the night or decreased bladder capacity can cause nocturia. A decreased bladder capacity can be seen in cystitis and allied conditions. Bladder outlet obstruction, such as that due to a hypertrophied prostate, can cause nocturia despite an increased bladder capacity; this is due to a large volume of residual urine when the patient retires at night. Conditions associated with polyuria (see below) can quite understandably, cause nocturia. Renal parenchymal disease is associated with tubular dysfunction and a diminished ability to concentrate urine; the osmotic load of solutes is not excreted completely during daytime, thereby necessitating the production of increased amounts of urine at night as well. This results in nocturia. In edema forming states (congestive heart failure, nephrotic syndrome, cirrhosis with ascites), nocturnal recumbency is associated with changes in tissue capillary pressures and mobilisation of edema fluid at night. This results in nocturia in these conditions.

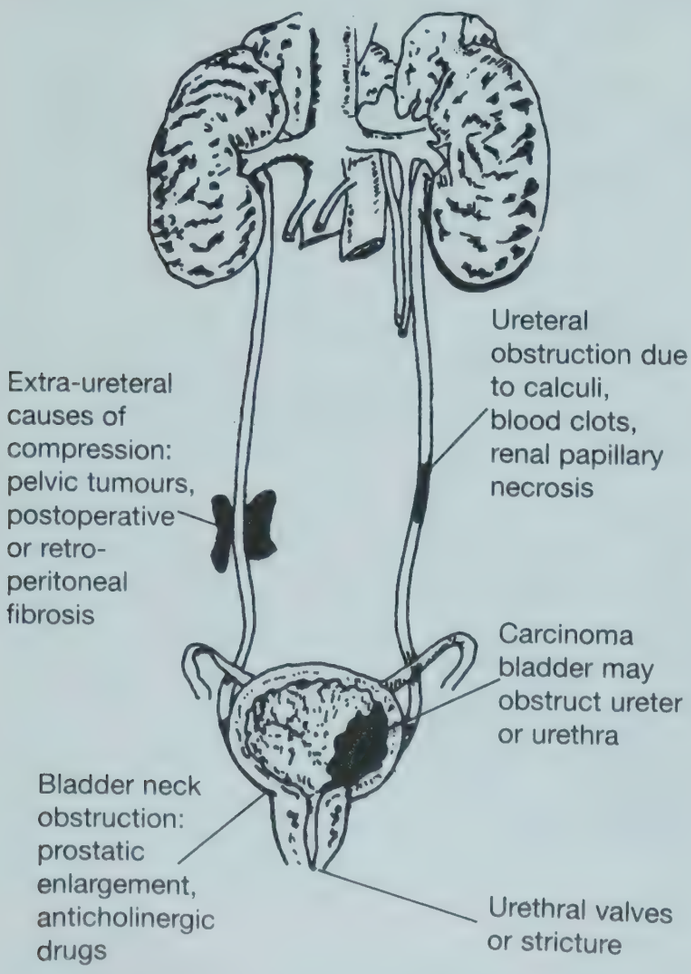


Fig 14.10 Causes of obstructive uropathy

Approach to a Patient with Polyuria

Polyuria is arbitrarily defined as urinary output exceeding 3 litres per 24 hours. If the lost fluid and solutes are not replaced, polyuria can become deleterious, culminating in hypotension and cardiovascular collapse.

Pathophysiology Polyuria may be a physiologic response to an osmotic load or an obligatory response to diuretic therapy. In diabetes mellitus, glycosuria produces a solute load resulting in an osmotic diuresis. Polyuria may also be a pathological response. Thus, *diabetes insipidus* is associated with a defect in renal concentrating ability (either due to lack of antidiuretic hormone — *central* diabetes insipidus — or due to a lack of responsiveness of the renal tubules to antidiuretic hormone–*nephrogenic* diabetes insipidus). This results in dilute urine and polyuria. The serum osmolality will, therefore, be increased due to the inability of the kidneys to conserve water. Polyuria may also be the result of compulsive drinking of water, a disorder referred to as psychogenic polydipsia. This disorder is usually associated with psychic disturbances. Since renal concentrating ability is undisturbed in

psychogenic polydipsia, water deprivation results in concentrated urine.

Diagnostic approach The history must be reviewed for symptoms of diabetes mellitus, excessive intake of water or drugs such as diuretics or lithium; the latter can cause an acquired nephrogenic diabetes insipidus. The next step is to determine urine and serum osmolality. If urine osmolality is more than or equal to serum osmolality, an osmotic diuresis (such as in diabetes mellitus) is likely and is investigated by obtaining a blood sugar profile. If urine is hypoosmolar with respect to serum, a fluid restriction test (*dehydration test*) is performed. If the urine becomes concentrated with fluid restriction, it can be concluded that the subject is drinking water excessively (psychogenic polydipsia). If the urine fails to become concentrated, the patient's response to vasopressin is determined. Lack of response suggests an end organ unresponsiveness to vasopressin classical of nephrogenic diabetes. Response to vasopressin with appropriate urinary concentration suggests a primary deficiency of antidiuretic hormone. (For details of tests see the following section.)

Approach to a Patient with Chyluria

Chyluria refers to the passage of chyle in the urine (milky urine).

Pathophysiology Chyluria is an uncommon manifestation of lymphatic filariasis in the filarial belt (parasitic chyluria) due to infection with *Wucheraria bancrofti*. On rare occasions, it may be related to other disorders that affect the retroperitoneal lymph nodes, such as tuberculosis and lymphomas, or due to congenital abnormalities of the thoracic duct.

In filariasis, the inflammation involves the paraaortic lymph nodes which act as an intermediate station for lymphatic flow from the intestines and the kidneys. Antegrade obstruction to lymphatic flow results in retrograde leakage into the lymphatics at the renal pelvis which may dilate and rupture, resulting in chyluria.

Diagnostic approach Chyluria may occur years after filarial infection and may often be sudden in onset and may be associated with straining. The other sequelae of filarial infection must be carefully sought (lymphangitis, hydrocele, elephantiasis, or lymphedema) in addition to evidence of other diseases such as tuberculosis and lymphoma. A differential diagnosis of milky urine must include severe pyuria usually associated with marked local symptoms, and passage of caseous material from cavitating renal tuberculosis, systemic features of which are usually present. Phosphates in the urine can also cause 'white urine' but dissolve on acidification. A simple test of urine with sudan red (that stains the lipid in the top layer) will confirm chyluria. Microfilaria may be looked for in the blood although they are usually absent.

Natural history Chyluria frequently undergoes spontaneous remission after the engorged, lymphatic vessel has ruptured, and runs a benign course.

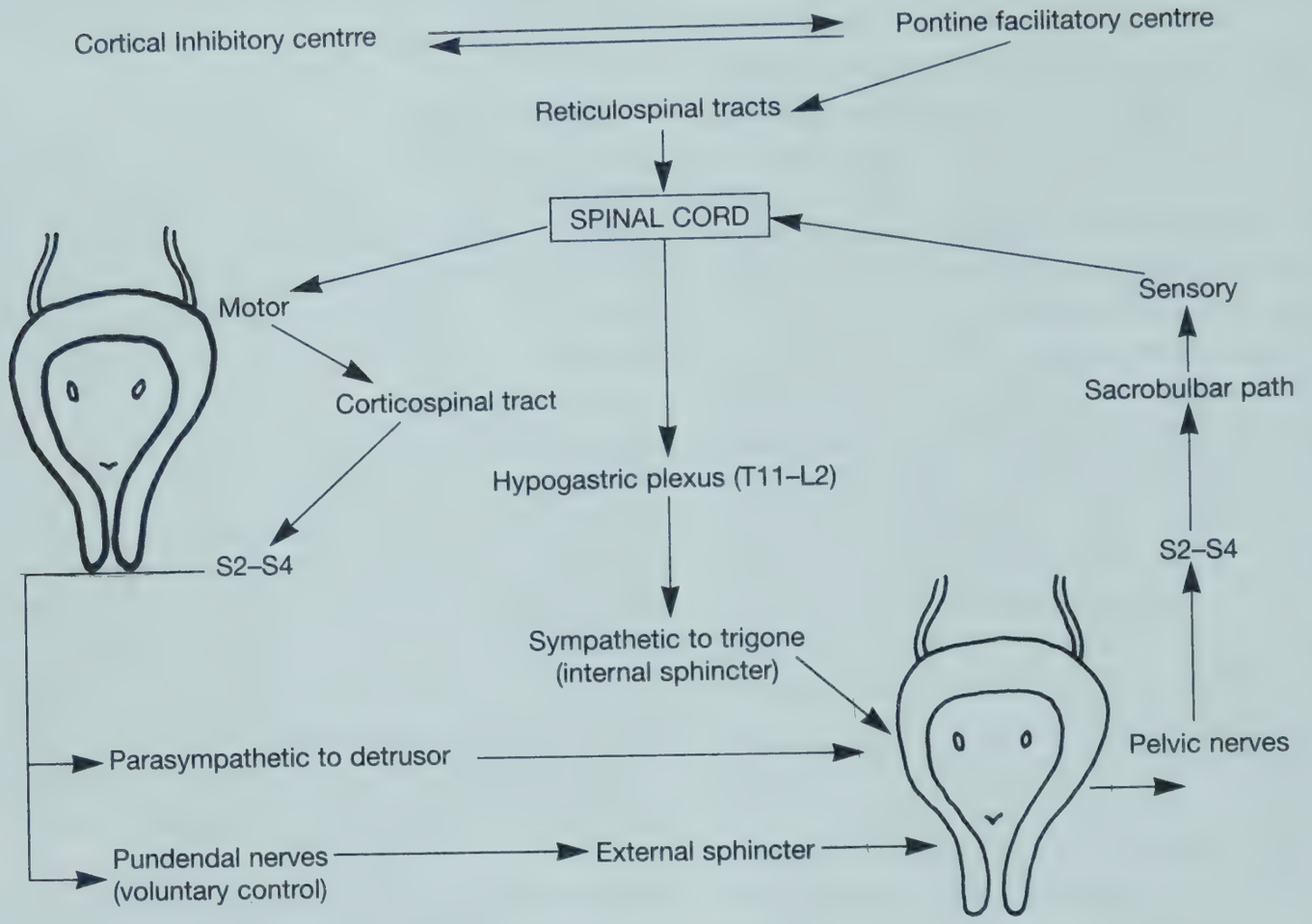
Treatment Unless active filarial disease is present, antifilarial drugs are not indicated and the disease tends to be self-limiting.

Approach to a Patient with Urinary Incontinence

Urinary incontinence refers to the inability to hold urine. Incontinence is a symptom and its causative factors are varied. Before we discuss the causes of urinary incontinence, an understanding of the normal physiology of micturition is essential.

Bladder physiology The innervation of the bladder is depicted in Fig 14.11. The normal act of micturition involves a sensation of bladder fullness (at a bladder volume of 400 ml,

Fig 14.11 Innervation of bladder



intravesical pressure >20 cm H_2O) carried by the pelvic nerves to the sacral cord and relayed to the cortical centres through a sacrobulbar tract. The cortical inhibitory centre withdraws its influence and the pontine facilitating centre sends messages relayed through the reticulospinal tracts to the thoracolumbar and sacral segments of the spinal cord. The act of micturition involves three coordinated synergistic acts: 1) relaxation of the external sphincter (under voluntary control, innervated by the pudendal nerves from the sacral cord: S2, S3, S4); 2) contraction of the detrusor muscle (parasympathetic nerves from the sacral cord); and 3) contraction of the trigonal muscles (under adrenergic-mediated sympathetic influence from the thoracolumbar cord: T11–L2) which occlude the ureteric orifices, thereby preventing the reflux of urine, and relax the so-called internal sphincter.

Pathophysiology of incontinence *Stress incontinence* is the involuntary loss of urine with any stress which increases intraabdominal pressure, such as coughing or straining. The problem is essentially not neurologic; the bladder neck and periurethral muscles are incompetent, (distal sphincter mechanism incontinence). It occurs in postmenopausal women who lose pelvic muscle tone or after pelvic surgery in which these muscles are damaged, and in the multiparous women in whom the anatomic position of the urethra and the vesicourethral angle (an important determinant of continence in women) are altered unfavourably (Fig 14.12).

Urge incontinence is the involuntary loss of urine when there is a strong desire to void. It occurs due to detrusor hyperreflexia (instability) and may be secondary to obstruction or cystitis (infective or non-infective).

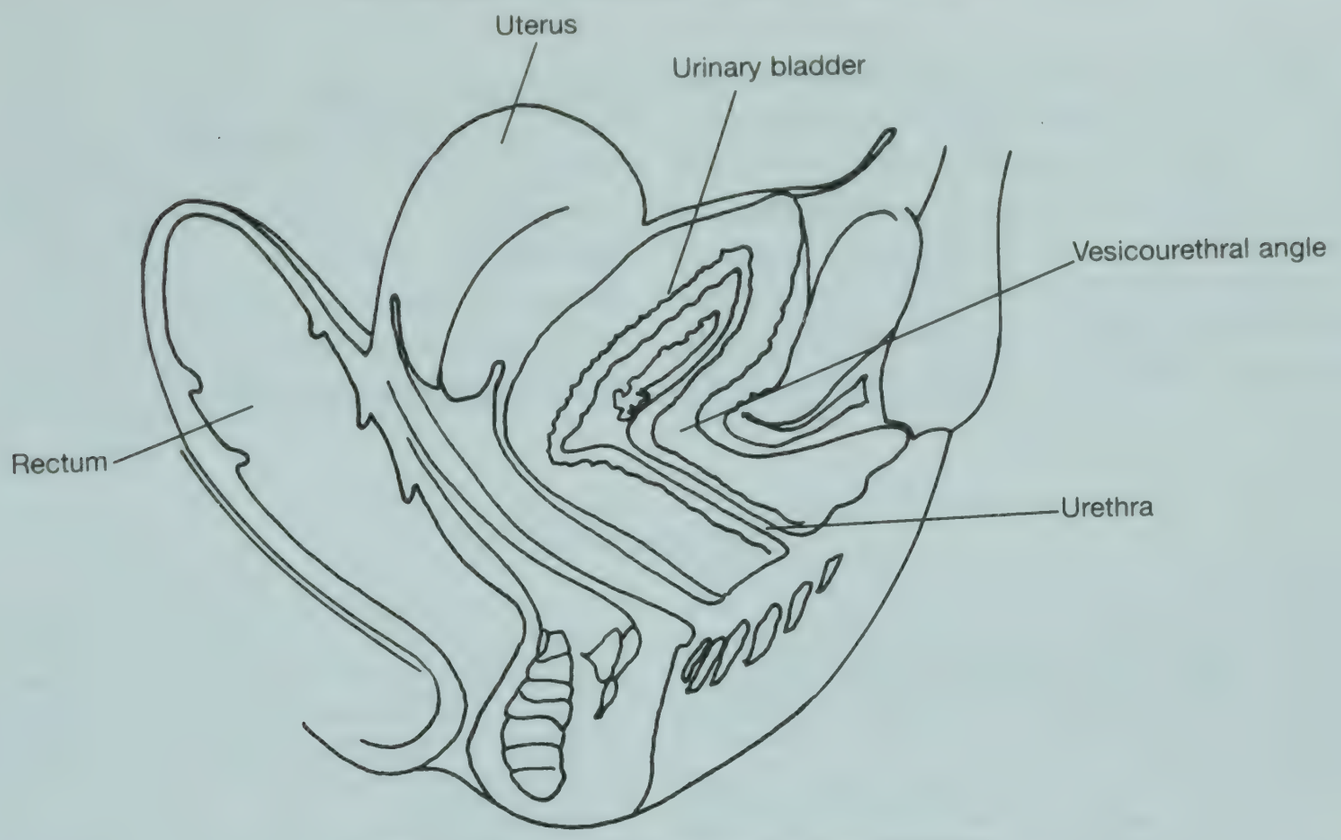


Fig 14.12 Urethra and vesicourethral angle altered

Reflex incontinence is a condition in which the subject passes small amounts of urine without any awareness of it. It is typical of a suprasacral cord lesion (upper motor neuron bladder), so that the afferent impulses of the bladder filling sensation are lost along with the supraspinal influences which ensure detrusor-sphincter synergism. As a result, a hypercontractile detrusor contracts at the same time as the external sphincter (dyssynergia).

Overflow incontinence is characterised by reduction in the stream and force of micturition. Post-micturition dribbling may also occur. It may be caused by neurologic disorders such as destruction of the sacral cord or an autonomic neuropathy, which result in a hypotonic detrusor and therefore a large volume of residual urine in a flaccid bladder (lower motor neuron lesion). Non-neurologic lesions that produce bladder outlet obstruction may also cause overflow incontinence.

History and physical evaluation A detailed history characterising the type of incontinence is essential. A history of dysuria or frequency may suggest cystitis, as may a history of irradiation of the pelvis (radiation cystitis). The history may also suggest a systemic disorder such as diabetes which may have associated autonomic neuropathy. A careful enquiry about any neurologic disease must be made. Physical examination for any neurologic disease such as a spinal cord lesion, cerebrovascular lesion or autonomic neuropathy must be performed systematically.

Special investigations Apart from urinalysis, urine culture and blood chemistry, the help of a urologist may be sought for a series of tests referred to as urodynamic tests. These tests include cystometry, in which the intravesical pressure and detrusor activity can be assessed, and electromyography of the external urethral sphincter which tells us about the tone of the sphincter.

Treatment Broadly speaking, detrusor hyporeflexia (atonic/flaccid bladder) requires a cholinergic agent such as Bethanechol (40–150 mg/day). Detrusor hyperreflexia (spastic bladder) requires an anticholinergic agent such as probanthine (15–30 mg, two to

four times a day) or a tricyclic antidepressant (imipramine 100–200 mg daily in divided doses). Newer agents available for detrusor hyperreflexia include flavoxate and dicyclomine. If dyssynergia between the external sphincter and a hyperreflexic detrusor is the problem, the anticholinergic agents can be combined with dantrolene, diazepam or baclofen. Stress incontinence, which is due to a decline in proximal urethral adrenergic tone, may be treated with adrenergic stimulants like imipramine or a β-blocker like propranolol (β-blockers accentuate adrenergic activity throughout the body). Mechanical obstruction is to be dealt with surgically and cystitis treated with an appropriate antibiotic.

KEY CONCEPTS

Hematuria

- Common etiologies of hematuria include infections (30%; including TB), calculi (20%), urothelial cancers (15%), and miscellaneous causes (drugs or systemic disease).
- A history of the *duration* (longstanding: benign), *nature* (pain: calculi; painless: glomerulonephritis, cancer; dysuria: infection; pyuria: infection, calculi, TB; systemic symptoms: SLE, Henoch-Schonlein, purpura vasculitides), and *timing* (initial or terminal onset during micturition indicate urethral or prostatic source, respectively) yield helpful clues to the etiology.
- Urinalysis is vital. Red cell casts or dysmorphic cells in the urine indicate a glomerular source (glomerulonephritis, IgA nephropathy) of bleeding or *benign recurrent hematuria* (no proteinuria); presence of white cells in the urine may indicate an infection or renal calculus disease. Urine cytology, US/IVP and cystoscopy are also helpful in the diagnostic evaluation.
- Treatment depends on the underlying cause.

Oliguria

- *Oliguria* refers to a daily urine output less than 500 ml.
- It is important to obtain a detailed history to exclude intravascular volume depletion (GI losses due to diarrhea, vomiting or dysentery; blood loss; CHF, hepatic failure), recent surgery, administration of nephrotoxic medications, and prior renal disease (such as calculus disease). *Anuria* (<100 ml/day) suggests acute cortical necrosis, RPGN, or bilateral renal vascular or ureteric obstruction.
- The clinical examination must include an assessment of fluid status (dehydration, orthostatic changes in blood pressure, pulse rate), jugular veins (elevation in CHF), and check for the presence of a suprapubic or flank mass (obstructive uropathy).
- Urinary indices help differentiate *prerenal* causes from *renal* causes. An *FE_{Na} < 1%, BUN/creatinine ratio > 20, hypertonic urine* (U_{OSM} > *500 mOsm/kg*) and *U_{Na} < 10 mEq/L are suggestive of a prerenal cause of oliguria.* An ultrasound is helpful for excluding urinary tract obstruction.
- Treatment depends on the underlying cause (volume replacement for dehydration; relief of obstruction for postrenal causes, etc.)

Nocturia

- Nocturia is usually due to a reduced bladder capacity (infection, tumour, stone or obstruction), a polyuric state, or an edematous condition (CHF, nephrosis, cirrhosis).

Polyuria

- Polyuria refers to a daily urine output in excess of 3 litres. Polyuria may be due to decreased vasopressin secretion (*central* diabetes insipidus), failure of renal responses to vasopressin (*nephrogenic* diabetes insipidus: drugs, systemic disease, hypokalemia), related to solute diuresis (diabetes mellitus) or natriuresis (Bartter syndrome), or it may be the result of excess water intake (*psychogenic*).
- Hypernatremia often coexists. It is important to exclude diabetes mellitus. The *water deprivation test* is helpful. The *normal* response consists of U_{OSM}>700 mosm/kg and a urine volume < 0.5 ml/min. In *diabetes insipidus,* the U_{OSM} is < 200 mOsm/kg while the urine flow is >0.5 ml/min; further after an injection of 5 u of vasopressin, an increase of >9% in U_{OSM} identifies *central* diabetes insipidus; in *nephrogenic* diabetes insipidus, there is an increase of <9% in U_{OSM} after vasopressin injection. In *psychogenic polydipsia*, the U_{OSM} after deprivation is >400 mOsm/kg generally.
- DDAVP is the treatment of choice for central diabetes insipidus. In nephrogenic diabetes insipidus, thiazides may be helpful.

14.3 Diagnostic methods in renal disease

Microscopy of Urine

Normal and abnormal urine

Microscopic examination of a centrifuged normal urine specimen may reveal few white cells (<3–5/high power field, large with lobulated nuclei), an occasional red cell (<3–5/high power field, small without nuclei) and some hyaline casts. Renal tubular epithelial cells may also be seen (large but with compact nuclei, unlike the white cells). *Casts* are cylindrical elements consisting of a core which is a protein coagulum, and are formed and moulded by the shape of the renal tubules. The protein coagulum traps any tubular luminal contents within its matrix. *Hyaline casts* are clear structureless cylinders composed of a mucopeptide produced by the ascending limb of the loop of Henle (the Tamm Horsfall protein). These casts are found in normal urine, particularly if it is concentrated. *Cellular casts* may be red cell casts (red cells adhering to the surface of a hyaline cast) indicating hematuria of glomerular origin or white cell casts (white cells adhering to a hyaline cast) indicating glomerular or upper urinary tract inflammation and possible infection. When a cellular cast degenerates, a *granular cast* develops. Unless the specimen of urine is one collected after heavy exertion their presence in urine invariably indicates a significant renal pathology. When a granular cast in turn degenerates, it assumes a waxy look and is called a *waxy cast.* In chronic renal failure the distal tubules are dilated and wide. Hence the casts in this condition are referred to as *broad renal failure casts.* In the presence of lipiduria, *fatty casts* may be seen, as in the nephrotic syndrome. If several cellular elements are present in a urine specimen, that is, red cell casts, white cell casts, granular casts, this is referred to as a *telescoped urine deposit*[1] and is typically seen in systemic lupus erythematosus.

Leukocyturia

A quantitative estimate of excretion of urinary cells can be made using an Addis count (in a 12-hour or 2-hour urine collection). The normal values are about 200,000 RBCs and 200,000 WBCs per hour (red cell five million and white cells upto two million per 24 hours, casts upto 10,000 per 24 hours, almost always hyaline). The technique is laborious and hence of limited use. Leukocyturia may represent urinary tract infection or may be seen in other conditions (sterile pyuria) such as renal calculus disease, urinary tuberculosis, analgesic nephropathy or urethritis.

Biochemistry of Urine

Proteinuria

Normal urine contains less than 150 mg of protein per 24 hours for adults (values of upto 300 mg/24 hours may, however, be seen in a minority of healthy adolescents), consisting predominantly of albumin and tissue protein of

[1] Telescoped urine deposit refers to telescoping of the time course of nephritis, i.e., changes of acute, subacute and chronic glomerulonephritis are simultaneously present in the urine deposit.

renal-urothelial origin. Increased urinary excretion of protein is hence the most common and most easily detected evidence of renal disease. Urinary protein may be detected by heating an acidified urine specimen, addition of 20 per cent salicylsulphonic acid or a colorimetric pH sensitive dye-based dipstick test. The latter has an unusually high sensitivity (can detect 15 mg/dl protein in a concentrated specimen) giving rise to false positive tests. A positive qualitative test for protein leads to further evaluation with a quantitative estimate of 24 hours urinary protein excretion. A separate collection of the daytime urine and the overnight urine (after 10–12 hours of recumbency) gives a clue to the entity of orthostatic/postural proteinuria wherein the overnight urine is almost protein free, proteinuria occurring during daytime in the erect posture.

The mechanisms of proteinuria are fourfold.

1. *Physiologic* proteinuria occurs in febrile states, after heavy exercise or after seizures and reflects the transient alteration in renal hemodynamics in these states.
2. *Overflow* proteinuria reflects states with increased endogenous production and therefore increased serum levels of protein, for example, abnormal production of immunoglobulin light chain fragments, 'Bence Jones protein' in plasma cell disorders.
3. *Glomerular* proteinuria is due to altered permeability of the filtration barrier. In some cases the proteinuria is selective, that is, it consists of low molecular weight proteins, predominantly albumin (<70,000 daltons). In other cases where the disruption of the filtration barrier components is more extensive, proteins with higher molecular weights also leak. This is known as non-selective proteinuria. Criteria and indices based on the selectivity of proteinuria are too laborious for routine clinical use and basically indicate the severity of glomerular damage.
4. *Tubular* proteinuria is seen in tubulo-interstitial disease and is characterised by small amounts of protein leak usually <1 g/24 hours. There is a marked increase in urine β_2 -microglobulin (a tubular protein of molecular weight 14,000 daltons) relative to albumin.

Tests of Glomerular Function

Blood urea

Urea is synthesised by the liver from ammonia derived from the catabolism of endogenous and dietary proteins and amino acids (the urea cycle). In the kidneys, urea is filtered, reabsorbed and secreted. Hence, in renal excretory failure blood urea rises. The glomerular filtration rate must, however, be reduced by more than 60 per cent before blood urea levels are elevated. Conditions which increase reabsorption of blood urea (dehydration) or catabolism of body protein (infections, gastrointestinal hemorrhage, steroid therapy, burns, high protein diet) can cause increases in blood urea without renal impairment.

Serum creatinine

Creatinine is an end product of creatine metabolism, and its endogenous production correlates with the muscle mass. In the kidneys, creatinine is both filtered and secreted so that creatinine clearance would exceed the glomerular filtration rate. The secretory component of creatinine excretion increases further in moderate degrees of renal failure, so that creatinine clearance may overestimate the glomerular filtration rate. The simplicity of the test, however, renders creatinine clearance invaluable in the follow-up of a patient with renal failure, as a rough index of the glomerular filtration rate. Creatinine clearance is given by the formula

$$C_{cr} = \frac{UV}{P}$$

where C_{cr} = volume of plasma cleared of creatinine per minute (ml/min); U = Urine concentration of creatinine (mg/100 ml); V = Volume of urine produced (ml/min); P = Serum creatinine (mg/100 ml)

Normal values of creatinine clearance range from 100 to 150 ml/minute in men and 85 to 125 ml/minute in women.

It must be remembered that creatinine clearance normally declines with ageing. It may be 50 per cent of normal at 70 years in the absence of renal disease.

Tests of Tubular Function

Proximal tubules

These tests comprise the measurement of glucose and bicarbonate reabsorption and urinary amino acid excretion. Thus, proximal tubular disorders must be suspected when glycosuria, aminoaciduria and bicarbonaturia occur alone or in combination.

Distal tubules

Tests of concentration dilution ability A simple test for assessing solute concentration in urine is its *specific gravity* measured with a hygrometer. This, however, is a crude estimate of osmolality. In chronic renal failure the specific gravity is fixed at about 1.010 which is isotonic with plasma: this is referred to as isosthenuria. The maximal concentrating ability is assessed by restricting fluids for 16–20 hours with a consequent weight loss of 3–5 per cent of the body weight. Additional information is obtained by an injection of 5 units of vasopressin after three consecutive hourly collections of urine which have shown no further increase in osmolality. Under these test conditions, a normal person secretes enough antidiuretic hormone (ADH) to reabsorb water at the distal tubules and to elevate urine osmolality to 900 mOsm/kg (specific gravity = 1.023). The injection of vasopressin does not alter osmolality further as the endogenous antidiuretic hormone is at its maximum effect already. In central diabetes insipidus, in which secretion of ADH is defective, the dilute urine becomes concentrated after the injection of vasopressin. In nephrogenic diabetes insipidus, in which the secretion of ADH is normal but the renal tubules are hyporesponsive to ADH, the dilute urine at the end of the test cannot be concentrated even by the injection of vasopressin.

The diluting capacity is assessed by administering a water load of 20 ml/kg to a fasting subject. A normal subject can achieve dilute urine with a specific gravity of 1.002 corresponding to an osmolality of 80 mOsm/kg at six hours. This test has very little clinical utility.

Test of urinary acidification In this test, a mild metabolic acidosis is induced by oral administration of ammonium chloride (100 mg/kg dose) and urine specimens are collected hourly. A normal distal tubular function allows excretion of at least 30 per cent of this acid over 6–8 hours and consequently the urine pH declines to less than 5.5. Failure to lower the urine pH below 5.5 points to an inability of distal tubules to excrete acid as in distal renal tubular acidosis.

Urinary Electrolytes

Urine sodium concentration is useful in the evaluation of the hyponatremic or oliguric subject. When hyponatremia is due to loss of volume, the kidneys under the influence of ADH and aldosterone absorb sodium avidly and urinary sodium concentration is less than 10 mEq/L. In aldosterone deficiency, renal salt wasting occurs and urinary sodium is >20 mEq/L. In the syndrome of inappropriate ADH secretion (SIADH) too the urinary sodium is >20 mEq/L in the presence of hyponatremia. When oliguria is due to prerenal causes, the kidneys, which are functioning normally, absorb sodium avidly and urinary sodium concentration is generally less than 20 mEq/L. In oliguria due to renal causes such as acute tubular necrosis, the kidneys fail to absorb sodium and urine sodium is 20–40 mEq/L.

Urine potassium concentration enables us to determine whether hypokalemia is due to renal

or extrarenal losses. If the loss is due to extrarenal causes like vomiting, the kidneys avidly reabsorb potassium, and urine potassium levels are less than 10 mEq/L. In renal potassium wasting, either due to intrinsic renal disease, diuretics or excess mineralocorticoids (Conn syndrome), urinary potassium levels exceed 20 mEq/L.

Similarly, in metabolic alkalosis, which is most often due to gastrointestinal or renal chloride loss (hypochloremic metabolic alkalosis), urine chloride less than 10 mEq/L points to a non-renal loss and a likelihood of response to volume replacement and chloride repletion. A urine chloride greater than 10 mEq/L suggests urinary chloride loss (diuretic induced, Bartter syndrome, corticosteroid effect).

Renal Imaging

Plain X-ray KUB

Also called a scout film, an X-ray film after adequate purgation may reveal the number and size of kidneys and any calcification. Calcification may be medullary (nephrocalcinosis), in the cortex or in the pelvicalyceal system (calculus disease).

Intravenous urogram (IVU)

The excretory urogram, also known as an intravenous pyelogram (IVP), is performed by intravenous injection of a radio-opaque iodinated contrast material. The initial phase which appears within one to two minutes is the *nephrogram* in which the renal parenchyma is seen. The *pyelogram* phase, which occurs within five minutes, visualises the major collecting duct system. Thus the IVU gives information regarding the number, size, shape and position of the kidneys and the patency of the excretory system. Bilateral small kidneys are most often due to a chronic glomerulonephritis whereas unilateral small kidneys may occur due to congenital hypoplasia or due to postinfarction shrinkage.

Bilateral enlarged kidneys with a 'spidery' elongated calyceal system suggest polycystic renal disease whereas a unilateral enlarged kidney should arouse suspicion of a mass lesion or hydronephrosis. It must be remembered that apart from the five per cent incidence of adverse reaction to contrast media, there is an increased risk of precipitating renal failure when an IVU is performed in the diabetic population.

Ultrasonography

Ultrasonography has largely superseded IVU for the evaluation of renal size, shape and position, for the evaluation of perinephric lesions, renal mass lesions and renal calculi, and for assessing the degree of hydronephrosis. Ultrasonography can differentiate between cystic, solid and mixed lesions, and polycystic kidney disease has a distinct sonographic appearance. Ultrasonography can assess obstructive uropathy by providing information regarding prostatic enlargement and by estimating the post-voiding residual volume of urine. Although the technique tends to underestimate renal size with respect to IVU, it has the advantages of being safe, painless, non-invasive and can be repeated when required.

Radionuclide renal imaging

Radionuclide studies help in functional imaging whereas ultrasonography helps in anatomical imaging. In dynamic scintillation imaging, a radiopharmaceutical agent (the commonest is ^{99m}Technetium diethylene triamino pentaacetic acid–DTPA) is injected intravenously and the time course of appearance and disappearance of regional radioactivity recorded (time-activity curve). It, therefore, demonstrates perfusion of both kidneys and areas of abnormal perfusion. It permits assessment of vascularity of space-occupying lesions and documents the presence of vesicoureteric reflux in children. A major advantage lies in the functional comparison of the two kidneys in disorders with asymmetric

renal dysfunction such as unilateral renal artery stenosis.

Computerised tomography

This technique permits detection of smaller lesions (upto 0.5 cm) which cannot be picked up by ultrasonography and permits accurate staging of renal neoplasms. It is also indicated where, due to technical reasons, ultrasonographic imaging is suboptimal.

Magnetic resonance imaging

This new technique is of special importance in evaluating major renal vessels for patency and tumour involvement.

Interventional Radiologic Procedures in Renal Medicine

These include *drainage procedures* where, under ultrasound guidance, the kidneys or the pelvis can be drained percutaneously and *vascular procedures* such as angioplasty of narrowed renal vessels and embolisation of feeder vessels to renal tumours (*angio-occlusion* or *embolotherapy*).

Renal Biopsy

A specimen of renal tissue can be obtained percutaneously using a trucut needle, preferably under ultrasonographic guidance.

The indications for renal biopsy include

1. heavy proteinuria or proteinuria with hematuria,
2. non-resolving acute renal failure,
3. renal transplant rejection, and
4. renal involvement in systemic disease, such as systemic lupus erythematosus.

The specimen is sent for light microscopy, immunofluorescence microscopy and, when required, electron microscopy, as for example in IgA nephropathy and Alport's disease.[1] The contraindications include a bleeding diathesis, a solitary functioning kidney and uncontrolled hypertension. Whereas microscopic hematuria is universal after a renal biopsy, gross hematuria (which is usually self-resolving) occurs as a complication in about one in ten patients.

[1] Alport's syndrome is hereditary nephritis with sensorineural deafness and associated ocular abnormalities such as spherophakia and lenticonus. Electron microscopy reveals an abnormally split glomerular basement membrane. In IgA nephropathy, electron microscopy reveals a very thin basement membrane.

KEY CONCEPTS

Urinalysis

- ➢ Normal urine is yellow in colour and the 24-hour urinary protein excretion is less than 150 mg.
- ➢ Urinalysis is a good guide to diagnose glomerular and systemic disease; this is accomplished by microscopic examination of the urine sediment, and by qualitative evaluation for the presence of protein, glucose, ketone bodies or blood.
- ➢ A reddish brown discolouration is seen in hematuria, hemoglobinuria, myoglobinuria and with the intake of certain drugs (such as phenolphthalein). *Casts* are cylindrical elements with a mucoprotein coagulum as the *matrix* (which traps tubular luminal elements); red cell casts are pathognomonic of glomerulonephritis while white cell casts indicate tubulointerstitial disease. Urine cytology may be obtained in patients with suspected urothelial neoplasms.
- ➢ Urinary osmolarity varies from 50–1200 mOsm/kg depending on the prior state of hydration. A value above 700 mOsm/kg in a random sample excludes significant tubulointerstitial disease.

Proteinuria

- ➢ Proteinuria refers to excretion of urinary protein in excess of 150 g/day (alternatively, a urine protein/creatinine>0.2). Causes of proteinuria include increased *glomerular permeability* (glomerulonephritis, diabetes, amyloid), failure of *tubular resorption* (heavy metals, Fanconi syndrome), increased *urothelial secretion* (Tamm-Horsfall protein), and *overflow* due to increased plasma levels (Bence Jones protein in myeloma).
- ➢ Symptoms associated with proteinuria depend on the underlying illness. Urine microscopy is vital: red cell casts indicate glomerulonephritis while the presence of

WBCs and tubular casts suggests tubulointerstitial pathology. Measuring the 24-hour urine protein excretion is important. When there is mild proteinuria without any evident cause, consider the possibility of *functional* (fever, exercise), or *orthostatic* (on standing in young males) proteinuria.

➢ Treatment of proteinuria depends on the cause. It is important to exclude any systemic disease. Consider obtaining a renal biopsy if proteinuria is >2g/day and there is no obvious cause.

Glomerular filtration rate

➢ GFR is the amount of plasma ultrafiltrate derived from blood over a specified time period. It is usually estimated from endogenous creatinine clearance (C_{Cr}). The normal C_{Cr} ranges from 100–125 ml/min. C_{Cr} varies with age, gender and body mass.

➢ Generally, GFR is not a very sensitive measure of early renal damage; only after loss of 50–75% of glomeruli is a clear decrease in C_{Cr} noted.

Tests of urinary concentration ability

➢ Urinary concentration ability is determined by measuring U_{osm} after 16–20 hours of water deprivation, and again after administration of 5 units of vasopressin.

➢ The normal response to water deprivation is an increase in urinary tonicity (U_{osm} >900 mOsm/kg). A decrease in urinary concentrating ability is seen in central and nephrogenic diabetes insipidus, tubulointerstitial disease.

Tests of urinary dilution ability

➢ The ability of the kidneys to dilute urine is evaluated by measuring U_{osm} and volume 6 hours after a water load (20 ml/kg).

➢ The normal response is that U_{osm} falls to <100 mOsm/kg and urine volume exceeds 80% of the water load.

Test of urinary acidification

➢ The normal pH of urine (fasting sample) is below 5.5. When 100 mg/kg ammonium chloride is administered, plasma bicarbonate drops below 20 mEq/L and the urine pH drops below 5.5; a failure of urinary acidification is seen in distal renal tubular acidosis.

Renal imaging

➢ *Intravenous urography* (IVU) is a technique used to visualise the kidneys and the lower urinary tract with the intravenous injection of an iodinated benzoic acid derivative (radiocontrast).

➢ IVU is useful for evaluation of patients with obstructive uropathy, those with hypertension (with a suspicion of a renovascular etiology), urolithiasis or recurrent urinary tract infections.

➢ *Retrograde pyelography* is useful for identifying the site and extent of ureteric obstruction while the micturating cystourethrogram is useful for evaluating the degree of vesicoureteric reflux.

➢ *Renal ultrasonography* has largely replaced the plain X-ray (KUB) for evaluation of renal size and position.

➢ US is useful for diagnosis of polycystic kidney disease, detecting renal calculi and complications such as hydronephrosis or perinephric abscesses and for the evaluation of renal masses (cystic vs solid; benign vs malignant). US is also specifically useful for guiding renal biopsy and for the follow-up of patients with renal transplants.

➢ *CT* is more expensive than US but is superior to the ultrasound for evaluating the character and extent of renal and retroperitoneal masses.

➢ *MRI* is an alternative to CT for evaluating renal masses, and for staging renal neoplasms. It can identify vascular malformations and also differentiate the contents of a cystic mass (hemorrhage vs infection).

➢ *Renal biopsy* (with electron microscopy and immunohistochemistry) is a useful technique in the following situations: acute renal failure of unknown etiology or prolonged duration, nephrotic syndrome in an adult, lupus nephritis, transplant rejection. It is contraindicated in the presence of a solitary kidney, uncontrolled hypertension or a coagulopathy and is unlikely to yield useful information in patients with bilateral small fibrotic kidneys.

➢ A radionuclide scan of the kidney can assess renal blood flow and dynamic renal function (rate of excretion of radiolabelled compounds). It is useful for evaluation of asymmetrical renal function (as in renal artery stenosis), and the vascular patency of renal transplants.

➢ Renal angiography (intraarterial or intravenous digital subtraction techniques) is useful for evaluating suspected renovascular disease.

14.4 Renal failure

Acute Renal Failure

Acute renal failure is defined as an abrupt deterioration in renal function with the accumulation of nitrogenous waste products in blood. It must be noted that there is no mention of urine output in this definition. Although the clinical hallmark of acute renal failure is *oliguria* (defined as <500 ml urine per 24 hours), the entity of *non-oliguric renal failure* is being increasingly recognised. In this condition, the urine output may be more than 500 ml/24 hours but the kidneys continue to malfunction and blood urea and serum creatinine levels increase. This entity may account for upto 40 per cent of all renal failure.

Causes Broadly speaking, there are three categories of causes of acute renal failure (Fig 14.13). *Prerenal* causes include conditions with hypovolemia (dehydration, blood loss, third space sequestration, burns), or low cardiac output (congestive heart failure, shock). *Postrenal* causes mainly include causes of obstructive uropathy which are bilateral (ureteral obstructions) or which affect the function of both kidneys (bladder neck or urethral obstruction). *Renal* causes include renovascular causes such as malignant hypertension, microangiopathies, eclampsia or vasculitis. Renal parenchymal causes include glomerular dysfunction (postischemic; pigment related, for example myohemoglobinuria; nephrotoxic, for example, drug related). The commonest causes of renal failure are ischemia and nephrotoxins. The prominent nephrotoxins are antibiotics (aminoglycosides, cephaloridine, amphotericin), heavy metals and iodinated contrast media.

Epidemiology In India, about 60 per cent of cases of acute renal failure occur in a *medical* setting, with diarrheal disorders accounting for an important 15 per cent, snake bites (with hemolysis and intravascular coagulation, especially in coastal south India) causing 10 per cent and another 5–10 per cent related to poisoning with substances such as copper sulphate. Malaria treated with primaquin in an individual with G-6 PD (glucose-6-phosphate dehydrogenase) deficiency can result in intravascular hemolysis and acute renal failure. This disorder is not uncommon in north India. Shigella dysentery has also been known to cause acute renal failure in children. Twenty per cent of cases are classified as *surgical* (related to surgery or surgical problems), with trauma accounting for about half of these. Importantly, *obstetric* causes contribute 20 per cent of all cases of acute renal failure, a vast majority being related to septic abortions and postpartum sepsis. Iatrogenic renal failure is also likely to be common though there are no figures available in India regarding the relative contribution of this factor.

Pathogenesis and natural history The prime targets of ischemic or toxic damage are the renal

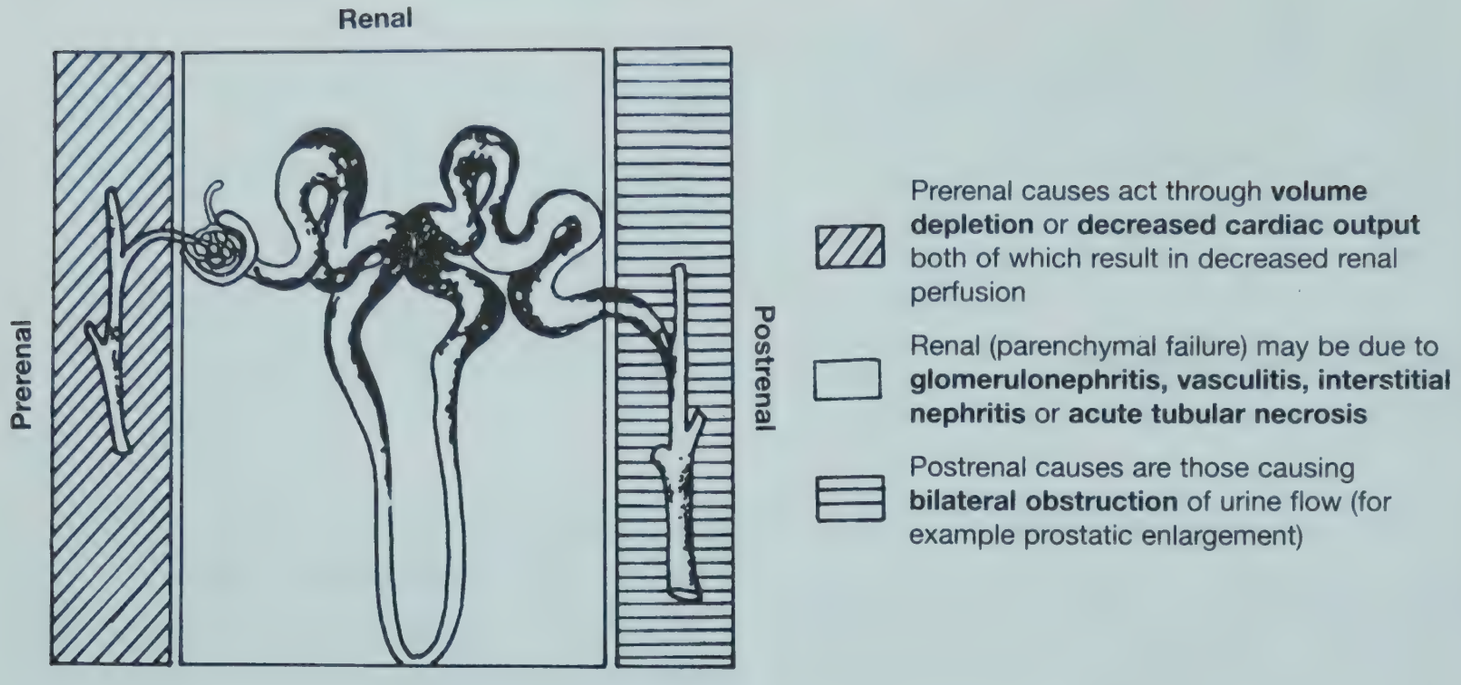


Fig 14.13 Three causes of acute renal failure

tubules, hence the term *acute tubular necrosis.* The distal convoluted tubules seem more susceptible (hence the older term *lower nephron nephrosis*) and the juxtamedullary part of the kidney is most susceptible as the PO_2 in that region is the lowest. The mechanisms of renal damage are several and since they act in concert their relative contribution may be difficult to assess. Glomerular mechanisms include an intense vasoconstriction of the afferent arteriole coupled with an altered glomerular permeability, both of which lead to a diminution in the glomerular filtration rate. Tubular mechanisms include mechanical intratubular obstruction by casts and a back leak of the filtrate into the peritubular capillaries both of which would diminish urine output.

Four phases in the clinical evolution of acute renal failure are now well-recognised. The *initial phase* is when the offending agent initiates renal injury. The duration of this phase may be hours (postischemic) or days (drugs). This phase is characterised by changes in urine composition rather than volume, since salt and water balance are well-maintained in the early course. Thus urinary excretion of urea and creatinine decrease whereas urine sodium may remain unchanged. The *oliguric phase* is characterised by a breakdown of salt and water balance and a consequent decrease in urine output. The urinary sodium frequently exceeds 20 mEq/litre and urine osmolality decreases (<350 mOsm/kg) as does urine specific gravity (<1.020). In this phase, blood urea levels steadily increase by 20–40 mg/dl and serum creatinine by 0.5–1 mg/dl daily. Hypercatabolic states like sepsis, burns, trauma and fever are associated with a more rapid rise of these parameters. Serum potassium levels also increase by 0.3–0.5 mEq per day in the non-catabolic patient. Asymptomatic mild increases in serum magnesium and phosphate levels may occur along with a slight fall in serum calcium levels. The increase in phosphate levels is related to decreased renal excretion. Inability to excrete the daily acid load leads to metabolic acidosis. Salt and water retention are associated with mild hypertension. The duration of the oliguric phase varies from one to three weeks. This phase may be associated with severe fluid overload resulting in pulmonary edema or other life-threatening complications such as severe metabolic acidosis, pericarditis, hyperkalemia or encephalopathy.

The *diuretic phase* follows the oliguric phase in the natural history of acute renal failure. The damaged tubules begin regenerating but are still

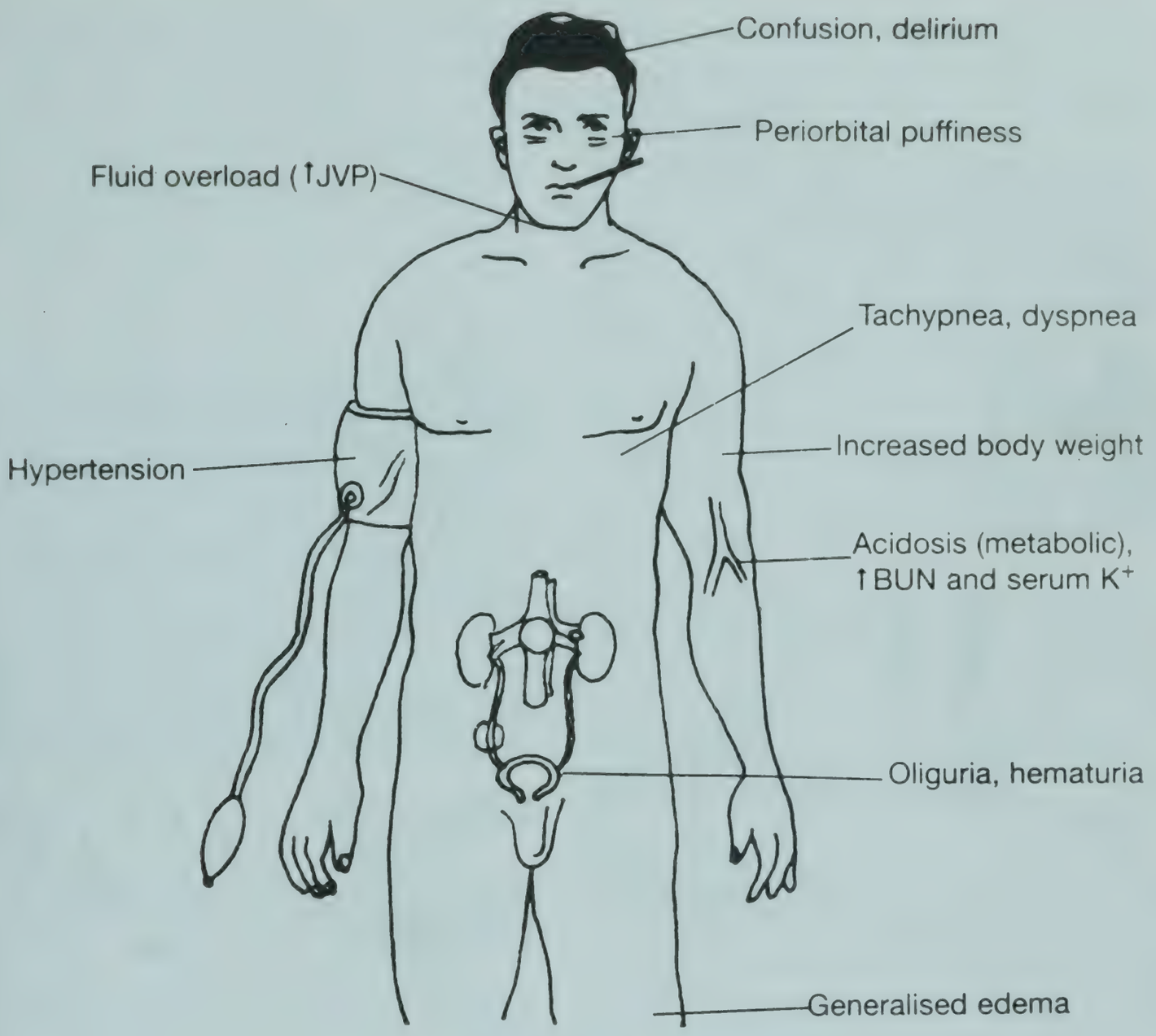


Fig 14.14 Clinical features of acute renal failure

unable to concentrate urine. Hence, the urine output steadily increases and even polyuria may occur (reflecting a tubular concentrating defect). Despite the attempt at normalisation of water metabolism, blood urea levels may rise even further reflecting persistent impaired glomerular filtration. The diuretic phase also varies in duration from one to two weeks. In this phase there is a considerable chance of electrolyte imbalance and this accounts for the fact that 25 per cent of all acute renal failure-related mortality occurs in this phase. The *recovery phase* is characterised by the functional recovery of most of the renal function. Distal tubular function may remain impaired for a longer period but this is of a minor degree and is, therefore, clinically unimportant. The three important prognostic factors are the length of the oliguric phase, the age of the patient and the presence of underlying renal disease.

Clinical features The clinical features have been discussed in detail above. The clinical picture would obviously vary with the setting in which renal failure occurs (Fig 14.14). However, irrespective of the setting, a very slow onset of renal failure, marked hypertension, persistent oliguria or significant macroscopic hematuria

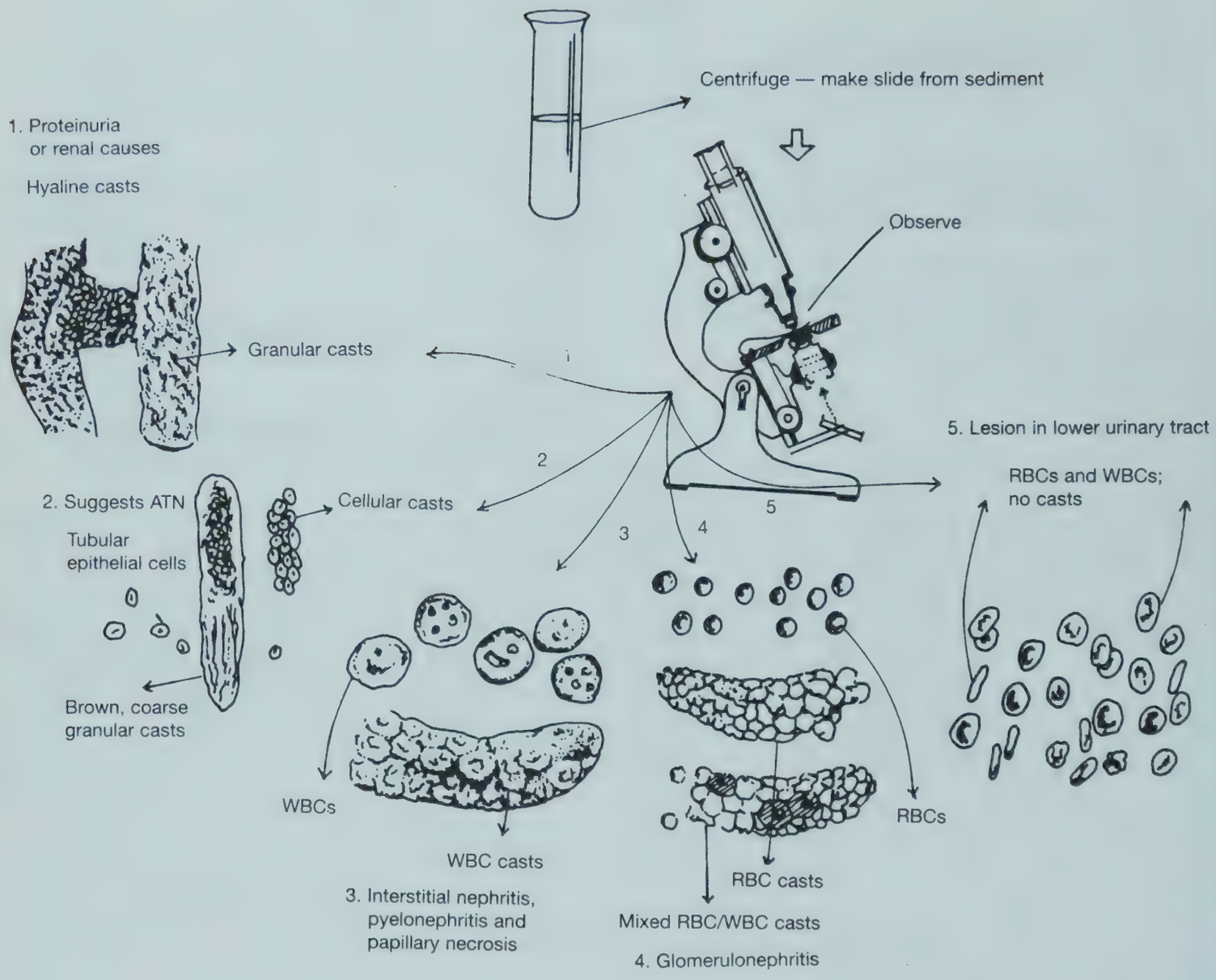


Fig 14.15 Urinalysis

are unusual in acute tubular necrosis and should alert the clinician to alternative diagnostic possibilities. Presence of significant growth retardation, significant anemia, peripheral neuropathy or bone pain strongly suggest the likelihood of an underlying chronic renal disease over which the acute renal insult is superimposed. Associated hemoptysis should make one suspect Goodpasture syndrome or systemic vasculitis. Associated jaundice raises the possibilities of a hepatorenal syndrome (usually with cirrhosis of the liver), toxic injury of both organs (poisoning) or infections (such as leptospirosis, or malaria with intravascular hemolysis).

Investigations The importance of urinalysis and various urinary indices has been discussed in

an earlier section on oliguria. To recapitulate, a high urinary Na, high fractional Na excretion and low urine osmolality indicate acute renal failure (Table 14.1). Brownish pigmented casts indicate tubular necrosis, red cell casts indicate glomerulonephritis, and eosinophils (identified with Hansel's stain) indicate an allergic interstitial nephritis (Fig 14.15).

Table 14.1 Useful differential laboratory values in ARF

	Volume depletion	*ARF (ATN)*
Urine osmolality (mOsm/kg)	>500	<350
U_{Na} (mEq/litre)	<10	>20
U/P urea ratio	>8	<3
U/P creatinine ratio	>40	<20
FE_{Na}	<1%	>1%

Management

Diet: Protein intake of 0.6 g/kg (using proteins of high biological value) with carbohydrate intake of 100 g/day is recommended. A hypercatabolic patient may require intravenous hyperalimentation. Salt restriction is dependent on the degree of edema; a 1–2 g net salt intake is advisable. The use of keto-analogues of essential amino acids is of doubtful benefit.

Fluid and electrolytes: In the initiating phase of the illness, a fluid challenge may be indicated if hypovolemia is likely to have occurred. An attempt may be made to convert oliguric renal failure to non-oliguric renal failure by using mannitol (2.5 ml/kg of a 20 per cent solution), furosemide (1.0 mg/kg bolus, or infusion 10–15 mg/kg/ hour) or dopamine 1–3 µg/kg/minute) alone or as a combination of the latter two drugs. Such a conversion definitely reduces morbidity; its benefit on mortality is less definite.

In the oliguric phase, the daily intake is restricted to the urinary output plus 400–500 ml, the latter representing insensible losses. The diuretic phase requires careful titration of oral electrolyte intake based on serum and urinary electrolyte levels.

Hyperkalemia is treated emergently (when levels are > 7.0 mEq/litre) with a combination of intravenous calcium chloride (10 ml of a 10 per cent solution over 3–4 minutes), 20 per cent dextrose (200 ml) with 20 units plain insulin and sodium bicarbonate (44 mEq, that is, one ampoule of a 7.5 per cent solution over five minutes followed by 150 ml over 24 hours). Non-emergent treatment with oral potassium binding ion exchange resins (25 g sodium polystyrene sulphonate orally every four hours) is started simultaneously.

Acidosis: Treatment of metabolic acidosis is required only when serum bicarbonate levels fall to less than 10 mEq/litre. Sodium bicarbonate can be given (at a dose of 1–2 mg/kg of a 7.5 per cent solution), taking care not to correct acidosis too rapidly to avoid the risk of tetany since ionised serum calcium may decrease dramatically.

Adjunctive therapy: Antacids, histamine-2 receptor blockade (cimetidine, ranitidine) may be of benefit if there is gastrointestinal bleeding or in the high-risk patient (given prophylactically). Hypertension can be treated safely with diuretics or calcium antagonists (nifedipine). All potentially nephrotoxic drugs must be avoided.

Dialysis: Indications for instituting dialysis include:

1. clinical deterioration with a change in sensorium,
2. severe acidosis with serum bicarbonate <10 mEq/litre,
3. life-threatening hyperkalemia (serum potassium >7.0 mEq/litre),
4. rapidly rising blood urea (60 mg/day rise) or absolute levels >200 mg/dl,
5. severe fluid overload,
6. pericarditis, and

7. poisoning, where the offending agent is dialysable (barbiturate).

The choice of the mode of dialysis is discussed in a later section of this chapter.

Treatment of precipitating cause This includes antibiotics and dilatation and curettage of retained uterine products for septic abortion, alkalinisation of urine for sulfonamide precipitated failure and allopurinol for acute uric acid nephropathy.

Newer modes of therapy Newer therapeutic modalities include cytoprotective agents such as calcium antagonists and prostaglandin infusions. They are still being evaluated in clinical trials.

Prognosis The prognosis is closely linked to the setting in which renal failure occurs. Thus 'surgical', 'medical' and 'obstetric' renal failure have mortality rates of 60 per cent, 30 per cent and 15 per cent, respectively. In any setting, non-oliguric renal failure has a better prognosis than oliguric renal failure.

Prevention Preventive measures include prompt treatment of all gastroenteritis cases, proper hydration of any patient before IVU, avoidance of intraoperative hypotension by careful monitoring and avoidance of excessive use of non-steroidal antiinflammatory drugs and other nephrotoxic agents by the physician. Obstetric care must be hygienic and aseptic and the importance of health education and the availability of easy access to safe medical termination of pregnancy need to be recognised as this will reduce the incidence of septic abortions and their associated complications. In areas with high prevalence of G-6PD deficiency, ideally, the levels of the enzyme should be assayed before prescribing drugs such as primaquin, nitrofurantoin or sulfonamides.

Chronic Renal Failure

Chronic renal failure is characterised by a progressive and generally irreversible decline in renal function. Two other terms in this contex deserve mention.

Azotemia refers to the biochemica abnormalities such as elevation of blood ure or serum creatinine which reflect impaired rena clearance of these substances. *Uremia* denote the clinical syndrome of advanced renal failur with altered fluid and electrolyte balance an abnormal renal hormonal function.

Etiopathogenesis In India, the commones underlying cause of chronic renal failure i chronic glomerulonephritis which accounts fo roughly half (50 per cent) of the cases. Diabete mellitus and interstitial nephritis account fo 15 per cent each. The rest of the cases are relate to miscellaneous causes like polycystic disease obstructive uropathy, renal tuberculosi and renal amyloidosis. Hypertension with it attendant nephropathy accounts for 5–10 pe cent of all cases of chronic renal failure.

Pathophysiology and clinical features Chroni renal failure is associated with a globa dysfunction of glomerular excretion, tubula transport, acidification and concentratio mechanisms (Fig 14.16).

The various metabolic functions of the kidne and the influence of renal dysfunction on thes functions are discussed below.

Sodium homeostasis: The kidneys maintain normal sodium balance till the late stages o renal failure by virtue of the capacity of th remaining normally functioning 'intact nephrons to compensatorily hyperfunctio (*intact nephron hypothesis*). Terminally, whe the glomerular filtration rate falls belo 5 ml/minute, the extracellular fluid volum expands. At this stage, fluid overload develop with peripheral edema, systemic and pulmonar congestion and hypertension. Functional flo murmurs and cardiomegaly may appea simulating the clinical picture of congestive hear failure.

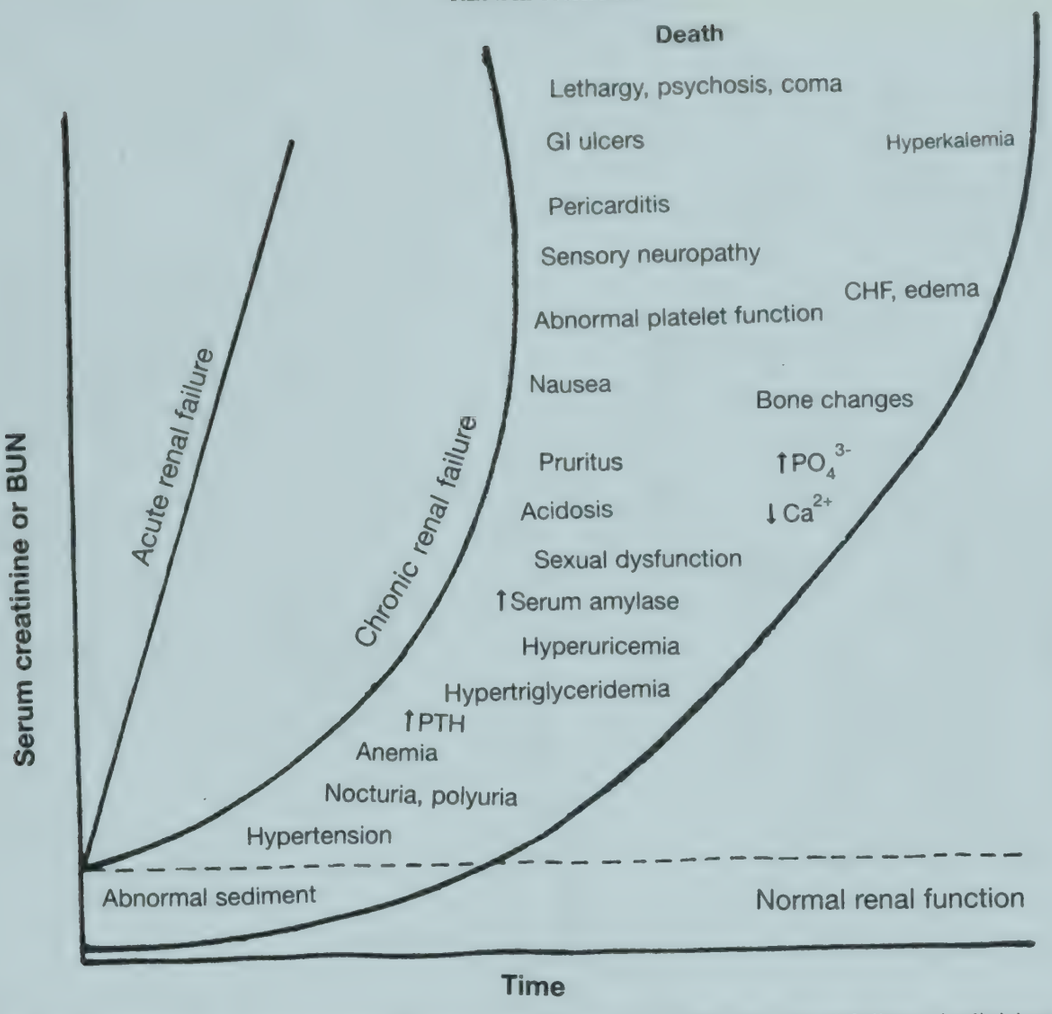


Fig 14.16 Schematic figure showing usual progression of chronic renal failure; individual patients may show considerable variation

Potassium homeostasis: The kidneys in chronic renal failure adapt by increasing the potassium secretion by the 'intact' nephrons. The gut also helps in this process by adapting and secreting more potassium into the intestinal fluids. Terminally, hyperkalemia occurs. Hyperkalemia tends to be aggravated by trauma, acidosis and blood transfusion.

Water balance: In the initial phases, the diminished tubular concentrating ability accounts for the excretion of a large amount of isoosmotic urine (isosthenuria); nocturia and polyuria, therefore, occur. Terminally, water is also retained along with sodium when the glomerular filtration rate falls below 5 ml/minute.

Calcium-phosphorus metabolism and the bone (Fig 14.17): One of the two major changes in the calcium-phosphorus balance which occurs in renal failure is a decrease in the intestinal absorption of calcium due to decreased 1, 25 dihydroxy vitamin D3 production by the kidneys. This results in fecal calcium loss, and the serum calcium level falls. The other major change is phosphate retention due to decreased renal excretion. The hyperphosphatemia in turn lowers serum calcium further and triggers off parathyroid hormone (PTH) secretion. The metabolic acidosis and raised PTH levels dissolve bone buffers and bone decalcification (osteoporosis) and remodelling-redistribution (osteitis fibrosa and osteosclerosis) results. Osteitis fibrosa is best seen radiologically as subperiosteal erosion of the phalanges and the clavicle; it occurs due to osteoclastic bone resorption. Osteosclerosis is evident radiologically as increased bone density of the upper and lower margins of the vertebrae. Aluminium in the dialysate fluid may be deposited in the osteoid seams resulting in aluminium-induced osteomalacia in patients on

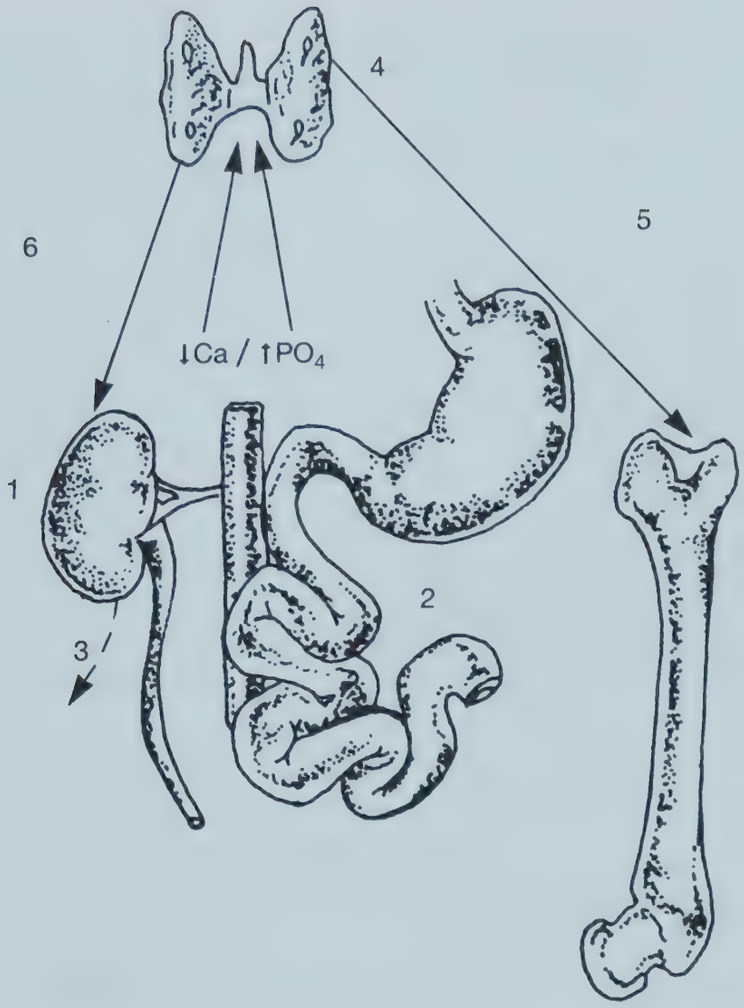


Fig 14.17 Calcium-phosphorus metabolism and bone. In chronic renal disease the kidney (1) is able to convert less 25-OH cholecalciferol to 1,25 dihydroxycholecalciferol. This reduces Ca^{2+} absorption from the gut (2). Diminished PO_4^{3-} excretion (3) leads to hyperphosphatemia. These changes in serum Ca^{2+} and PO_4^{3-} stimulate the parathyroid gland (4). Increased parathyroid hormone output *increases* calcium resorption from bone (5) and phosphate excretion by the kidney (6).

a chronic hemodialysis programme. The clinical counterpart of these changes (called *renal osteodystrophy*) is bone pain, diminished growth and proximal myopathy (probably related to altered vitamin D metabolism). When the calcium-phosphorus product (Ca multiplied by P) exceeds 60, the complex of calcium phosphate deposits in the subcutaneous tissues and cornea resulting in pruritus and band keratopathy, respectively.

Acid-base balance: The decreased ammoniagenesis at the distal nephron (normally an important mechanism of acid excretion) and renal phosphate retention account for an 'increased' anion gap acidosis.

This results in the recruitment of extrarenal buffering mechanisms, that is, the skeletal system, with its large reservoir of alkaline salts (calcium carbonate and phosphate). This enhances bone resorption.

Metabolic abnormalities Carbohydrate metabolism is altered with a peripheral resistance to insulin action and a consequent mild glucose intolerance. Lipid abnormalities arise due to depressed levels of the hepatic enzyme, lipoprotein lipase, which normally removes triglycerides from the circulation. This results in hypertriglyceridemia. An accelerated atherosclerosis results, and cardiovascular disease is therefore a common cause of death in these patients. Endocrine abnormalities, apart from elevated parathormone levels, include low estrogen and testosterone levels. This results in amenorrhea in women and reduced libido and impotence in men.

Cardiovascular abnormalities Hypertension is quite common in chronic renal failure (except in tubular disorders with salt wasting). Initially, it is vascular in origin (related to hyperreninemia and elevated angiotensin II levels). Subsequently, with fluid overload, volume-

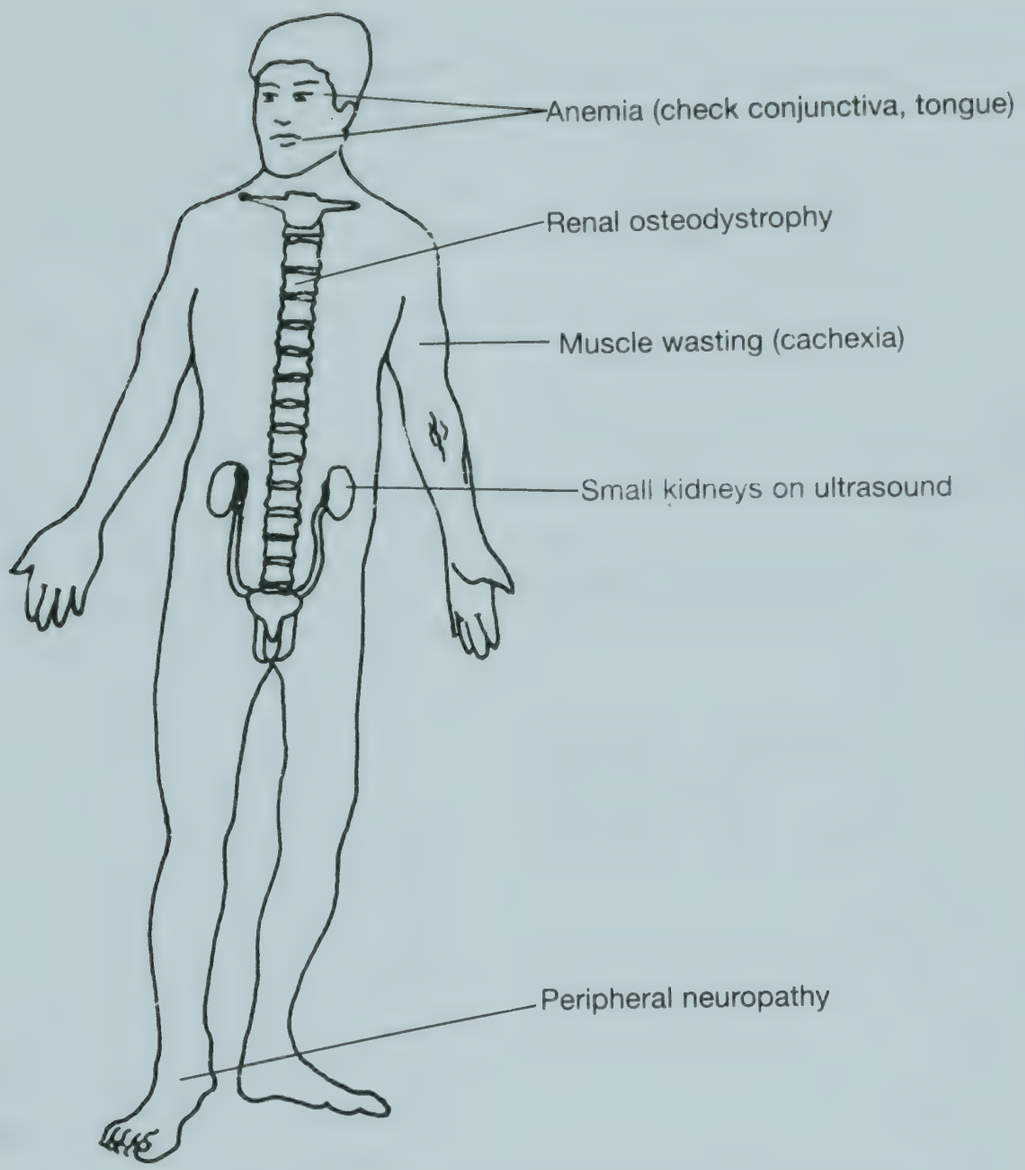


Fig 14.18 Clinical features which suggest that renal failure is chronic

dependent hypertension becomes an important mechanism.

Pericarditis may also occur, presumably due to retained metabolic toxins. It may be painful or painless, is commonly associated with a rub and occasionally causes tamponade.

The pericardial fluid is hemorrhagic due to the leakage of RBCs from the capillaries of the inflamed pericardium.

Hematologic abnormalities Anemia is an important manifestation of chronic renal failure. In fact, clinical symptoms such as malaise, dizziness and fatigue, so common in the uremic subject, may be related to anemia. The primary cause seems to be reduced synthesis of erythropoietin by the kidneys. Erythropoietin production has now been localised to the endothelial cells of the peritubular capillaries in the outer renal cortex. The anemia tends to be normocytic, normochromic. Other contributory mechanisms include a decreased red blood cell survival (resulting in hemolysis) and blood loss (due to platelet and coagulation function defects). Blood loss results in an iron deficient microcytic hypochromic picture, in addition. These subjects (especially subjects of a dialysis programme) tend to be folate deficient; a macrocytic anemia may, therefore, be superimposed. An enhanced susceptibility to infection occurs due to the decreased chemotactic ability of leukocytes in chronic renal failure.

Gastrointestinal abnormalities These include anorexia, nausea and a metallic taste early in the course of the disease. Increased gastric acidity (possibly related to elevated parathormone and gastrin levels) result in peptic ulceration. Superficial mucosal bleeding is fairly common and is related to the uremic state.

Neurologic abnormalities These include disturbed mentation with irritability, insomnia and attention lapses very early in the disease. In advanced renal failure, chronic sensorimotor peripheral neuropathy occurs and is generally taken as a clear-cut indication for initiating a dialysis or a transplantation programme.

Uremic toxins Several toxins have been suggested as being responsible for the symptoms of uremia. These include the *middle molecules* (polypeptides with molecular weight 1000–1500 daltons), the *guanidino compounds* (of which the guanidinosuccinic acid seems to interfere with platelet function) and parathormone itself.

Management of chronic renal failure

The following steps are advocated:

Establishing chronicity of renal failure (Fig 14.18): The presence of anemia, bone pain and radiologic bone disease, sonographically small kidneys or a peripheral neuropathy strongly suggest that the renal insufficiency is of longstanding duration. Normal-sized kidneys, however, do not rule out a chronic process and are seen in diabetes mellitus, progressive systemic sclerosis, systemic lupus, amyloidosis, polycystic kidney disease and a rapidly progressive glomerulonephritis.

Looking for reversible factors: Several factors hasten the progression of renal failure, and these are to be carefully sought and treated. They include urinary tract infection, obstructive uropathy, uncontrolled hypertension, nephrotoxic drug intake, low cardiac output and the presence of gout.

Looking for life-threatening complications: Presence of uremic encephalopathy, severe acidosis, severe fluid overload, hyperkalemia (serum K^+>7 mEq/litre), blood urea levels more than 200 mg/dl or serum creatinine more than 10 mg/dl indicate an urgent need for dialysis.

Conservative management: A proper diet which limits the protein intake to 0.6 g/kg body weight while ensuring enough calories, must be provided to the patient. This is because the few functioning nephrons have to hyperfunction to excrete the nitrogenous waste products–*glomerular hyperfiltration.* This hyperfiltration is in turn associated with renal vasodilatation and sclerosis of the functioning nephrons (glomerulosclerosis). Dietary protein restriction, therefore, seems to reduce the progression of renal failure. A consumption of 1–2 grams o sodium is permissible. Dietary phosphate and potassium are limited, and an oral fluid limit is established, based on daily losses. Keto-analogues of essential amino acids may be used, as they are aminated (using urea as a source of nitrogen) to form essential amino acids. The diet should be supplemented with folic acid. Vitamin D therapy is indicated if there is severe osteodystrophy; vitamin D forms with dihydroxylated versions (calcitriol) or a pseudo-1-(OH) version (dehydrotachysterol) may be used at doses of 0.25 µg and 0.5–10 mg daily, respectively. These forms do not require renal modification prior to their action. The anemia of chronic renal failure is best treated with intravenous or subcutaneous doses of recombinant erythropoietin (25 units/kg to 150 units/kg every 2–6 weeks, till the hematocrit increases upto 30 per cent). If erythropoietin is not available, androgens (oral fluoxymesterone or parenteral nandrolone) and blood transfusions may be used. These have the side effects of virilisation and iron overload, respectively.

Monitoring the progress of renal failure: The progress of renal insufficiency is monitored and the patient counselled regarding the

equirement for and the timing of a renal ransplantation or a chronic hemodialysis rogramme, if she is willing for the same.

Renal replacement therapy: This is discussed in detail in the following section.

Preventive measures

These include early recognition and treatment of essential hypertension, diabetes mellitus, renal calculus disease and anatomic abnormalities of the urinary tract. Nephrotoxic drugs must be avoided, and when their use is unavoidable, renal functions must be carefully monitored. At the earliest evidence of impaired renal function, they must be stopped and substituted with alternative non-nephrotoxic drugs.

Dialysis

Dialysis is the diffusion of substances between blood and the dialysis fluid (dialysate) across a semipermeable membrane.

Physiology and types of dialysis When blood and the dialysate are allowed to equilibrate across a semipermeable membrane, solutes will move from one compartment to another down their chemical concentration gradients. The rate of movement of the solutes will also be determined by their molecular weights (large molecules diffuse slowly) and the rate of blood flow. The semipermeable membrane may be the lining of the peritoneal cavity (peritoneal dialysis) or a non-toxic synthetic membrane compatible with blood elements (hemodialysis).

In peritoneal dialysis, the rate of blood flow through the peritoneal capillaries is constant and the volume of the dialysate is small since it is limited by the capacity of the peritoneal cavity. The dialysate contains hypertonic levels of glucose (1.5–4.25 per cent dextrose), isotonic levels of sodium and chloride and no potassium. Potassium can be added to the dialysate depending on the patient's needs. Similarly, by using the more hypertonic dialysate (4.25 per cent glucose) water removal can be enhanced. The clearance rate for urea is 20 ml per minute. Although the limiting factor is peritoneal blood flow (about 50–100 ml/minute), this mode of dialysis is better than hemodialysis for the removal of both larger molecules and 'middle molecules'. Typically, about twenty one-litre exchanges are made over 24–48 hours with half to one-hour 'dwell time' per exchange. A modification of the procedure which is increasingly popular is *chronic ambulatory peritoneal dialysis* (CAPD). In this modification, a permanent peritoneal dialysis catheter, called the *Tenckhoff catheter,* is inserted into the peritoneal cavity and the patient himself performs the exchange once every four hours during the day and once at night. Once the dialysate has been run into the peritoneal cavity, the empty but still connected fluid bags are tucked under the belt and the patient can be ambulatory for four hours (the time for complete equilibration between the dialysate and the peritoneal fluid). The dialysate is then run out into the bag which is disconnected and replaced by a new one. These transfers must be performed using a strictly aseptic technique.

In hemodialysis, an artificial membrane (of cellulose or polysulphone) is employed and a pumping device pumps in the blood at a rate of about 250 ml/minute. The dialysate is pumped in a counter-current direction at a higher rate (500 ml/min). The dialysate composition is similar to that in peritoneal dialysis but contains potassium (0–4 meq/L). This is to prevent a very rapid fall of potassium (as is likely if the dialysate were potassium-free). Calcium levels in the dialysate fluid are higher than in blood as most patients with chronic renal failure have a negative calcium balance. The dialysate contains acetate which diffuses across the membrane and is metabolised to bicarbonate, thus correcting the acidosis. Bicarbonate was earlier avoided as it tends to precipitate the calcium; as acetate was seen to cause hypotension during the dialysis, a modification called bicarbonate dialysis has now been evolved. The hydrostatic pressure within

the hemodialysis can also be raised to achieve optimum 'ultrafiltration'. An obvious disadvantage of hemodialysis is that it requires the patient to be hemodynamically stable. This has been circumvented by the use of high efficiency dialysers which are effective at low blood flow rates (*continuous arteriovenous hemodialysis)*. For chronic hemodialysis, a permanent vascular access is necessary. This may be fashioned with a conduit, using a native vein or a prosthetic tube, between an artery and a nearby vein on the forearm. The urea clearance achieved with hemodialysis is about 150 ml/minute. Hemodialysis requires heparinisation during the procedure. It immobilises the patient for about four hours, 2–3 times a week.

Procedure and timing The best timing for the initiation of dialysis is when conservative management of renal insufficiency becomes inadequate but before the development of uremic symptoms or target organ damage (neuropathy or bone disease). The financial aspects and the effectiveness of the dialysis programme with its advantages and disadvantages must be discussed with the patient and her family.

Simple peritoneal dialysis is reserved for the patient with acute renal failure who has a contraindication to anticoagulation or has hemodynamic instability. Also, if hemodialysis is not available, peritoneal dialysis can be used. If the patient is hypercatabolic, the rapid rate of rise in nitrogenous wastes cannot be managed by peritoneal dialysis. If he has had a recent abdominal surgery or peritoneal infection in the past, the fluid will collect within pockets of thickened peritoneum. In patients with underlying lung disease, the elevation of the diaphragm during peritoneal dialysis may result in basal atelectasis and respiratory distress.

For the patient with chronic renal failure, the choice is between an intermittent hemodialysis programme and chronic ambulatory peritoneal dialysis (CAPD). Ambulatory peritoneal dialysis is especially preferable in the diabetic patient who may have a problem of vascular access and in whom the diabetes itself can be optimally controlled by intraperitoneal insulin injections (without repeated subcutaneous injections). It however, requires patient motivation and carries a small but definite risk of bacterial peritonitis due to contamination during the exchange of bags.

Hemodialysis requires fashioning of a fistula or a graft for vascular access; the latter may become infected and serve as a source of bacteremia. Rapid shifts in solutes during hemodialysis result in neurologic disorientation referred to as a *dialysis-dysequilibrium* syndrome. Rarely, a chronic progressive dementia called *dialysis dementia* may develop in a patient on chronic hemodialysis, presumably related to the aluminium content of the dialysate water. Hemodialysis is also not as good as peritoneal dialysis for the removal of middle molecules. Abnormalities of lipid metabolism, anemia and sexual dysfunction may not be corrected but may worsen on dialysis. The patient on chronic dialysis is also prone to protein and folate deficiencies (water soluble vitamins are lost in the dialysate).

Renal Transplantation

Renal transplants are of two types: 1) from cadaveric donors (following brain death due to trauma, subarachnoid hemorrhage) where the kidneys are stored at 4–6°C and perfused constantly with cold saline, and 2) from living donors, who may or may not be related to the recipient.

Immunology The donor and the recipient must be histocompatible. The surface antigens on their leukocytes, lymphocytes and cells must be sufficiently similar, lest the recipient immune system should recognise the transplanted kidney as non-self and launch an immune attack on it. The sixth human chromosome carries a combination of genetic loci coding for genotypes for class I (A,B,C) antigens and class II (D)

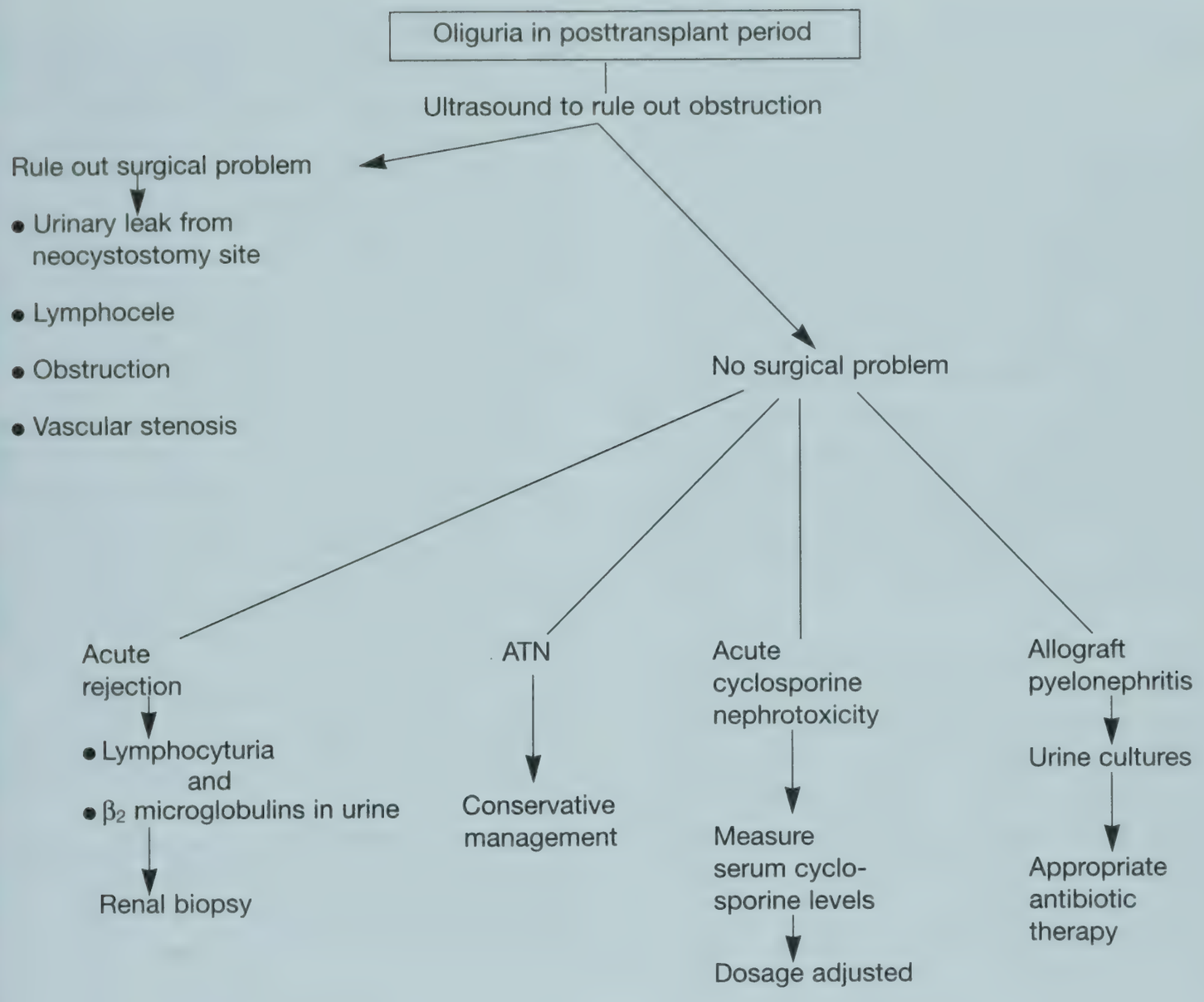


Fig 14.19 Approach to a post-renal transplant patient with oliguria

antigens. This is known as the *major histocompatibility locus.* Matching for A, B, C and D, DR antigens is ensured by specific specialised tests on the donor and the recipient. In this context, ABO blood group compatibility and D/DR compatibility seem to be of the greatest importance. Preoperative blood transfusions to the recipient seem to improve transplant survival.

After transplantation, the donor is placed on a protocol of immunosuppressive therapy, which may be any one or some combination of glucocorticoids, azathioprine, cyclosporine or antithymocyte globulin. With good immunosuppression, the survival rate of the cadaveric kidney is now approaching that of the live donor kidney. Despite these protocols the donor immune system can reject the transplanted kidney either immediately after surgery (early rejection) or later (chronic rejection). This rejection may be hyperacute, that is, intraoperative (when it may be due to pre-sensitisation of the recipient against the donor) or it may be in the first week after transplantation. It is then called acute rejection and is a cell-mediated immune response against the foreign donor cells. In this crisis period, rejection needs to be clinically differentiated

from acute tubular necrosis (posttransplant). The graft kidney, being placed more superficially in the loin, can be biopsied to make this differentiation. Acute rejection is treated with pulse methyl prednisolone and an intensification of the immunosuppressive regimen (Fig 14.19).

An antibody mediated late or chronic rejection may set in much later with the histology being one of glomerular arteriolar intimal hyperplasia. Chronic rejection is more common with cadaveric transplants and can lead to end stage renal disease, necessitating retransplantation. The immunosuppressive therapy itself is associated with side effects such as infections with opportunistic pathogens and the risk of developing lymphoreticular malignancies.

Relevance in the tropics Renal replacement therapy is limited in tropical countries by the complex interplay of several factors. Traditional beliefs and fatalistic attitudes of the family members often delay treatment. Dialysis and transplantation programmes are quite expensive and often beyond the reach of the common people. Technical sophistication for both hemodialysis programmes and transplantation is limited to a few hospitals in major cities. The lack of reliable, regular transportation and the nature of employment may dissuade the patient from opting for a chronic hemodialysis programme, apart from the financial burden of the treatment. The moral and social support which a candidate for a hemodialysis or transplantation programme requires, is not easy to find either. CAPD circumvents some of these drawbacks, but the risk of peritonitis is higher in a context of poverty and illiteracy.

However, with greater health education, attempts to increase dialysis facilities and the participation of voluntary charity organisations, these problems can, hopefully, be resolved.

On the brighter side, in a closely-knit society live, related donors (parents, siblings, children) are easier to find. Such transplants have the maximum chance of success.

Live, unrelated transplants should be discouraged as the chances of transplant survival are lower and also because an unethical trade in organs may ensue.

Inadequate awareness regarding organ donation and the poor facilities for tissue banking have made cadaveric transplants a rarity in India.

KEY CONCEPTS

Acute renal failure

- ARF is an abrupt decrease in renal function associated with increasing *azotemia,* with or without *oliguria;* if oliguria is absent (in 40%) the term *non-oliguric* renal failure is used. Non-oliguric ARF generally has a better prognosis.
- Etiologies of ARF include *prerenal* causes (reduced intravascular volume: hemorrhage, sepsis, dehydration; decreased perfusion: CHF; third space sequestration: ascites) *renal* causes (glomerulonephritis; acute tubular necrosis: ischemia, drugs; vascular lesions), and *postrenal* causes (obstruction: intrarenal [crystals], extrarenal [calculi, tumour])
- A thorough history, physical examination and urinalysis are vital. Acute Tubular Necrosis (ATN) has four phases: an *initiation* phase, a subsequent *oliguric* phase (10–14 days), a *diuretic* phase and a terminal phase of *recovery. Anuria* may suggest one of the following: acute cortical necrosis, RPGN, bilateral renal arterial occlusion, or bilateral ureteral obstruction. Red cell casts in the urine sediment suggest glomerulonephritis, PMN casts suggest interstitial nephritis, brown cellular casts suggest ATN while hyaline casts suggest prerenal cause. Urinary indices of sodium excretion, and BUN/ creatinine help differentiate three types of causes of ARF. *Ultrasound* is useful for assessing kidney size (excluding underlying chronicity) and for excluding urinary tract obstruction.
- Management consists of treating the underlying cause, targeting potentially reversible factors (volume

obstruction, antibiotics for any infection), establishing urine output (trial of furosemide or mannitol for converting oliguric to non-oliguric renal failure), reducing dietary protein and monitoring serum creatinine and serum electrolyte levels. *Indications for dialysis* include: severe acidosis, hyperkalemia, volume overload, encephalopathy, pericarditis and a rapidly rising serum creatinine level.

Chronic renal failure

➢ The following sequential decline in renal functions is seen in CRF: reduced renal reserve (35–50% of normal GFR) → azotemia (20–35% normal GFR) → uremia (<20% normal GFR) → ESRD (C_{cr}<5 ml/min)

➢ Causes of CRF include chronic glomerulonephritis, tubulointerstitial diseases, systemic diseases (diabetes, hypertension). Possible uremic toxins include urea and *guanidino compounds.*

➢ Clinical features are diverse due to involvement of several organ systems. *Gastrointestinal* symptoms include anorexia, nausea, vomiting and dyspepsia; *cardiovascular* manifestations include hypertension, pericarditis, fluid overload, accelerated atherosclerosis and dyslipidemia. Cardiovascular disease represents the most common cause of death; *neurologic* features include muscle twitches, cramps and peripheral neuropathy; *skeletal* symptoms include bone pain and proximal myopathy; pruritus may be prominent in CRF; *hematologic* findings include normocyctic normochromic anemia and increased tendency of bleeding, *endocrine* manifestations include amenorrhea and growth retardation.

➢ *Metabolic disturbances* include acidosis, hyperkalemia, sodium and water retention; hyperparathyroidism with hypocalcemia, hyperphosphatemia, reduced Vitamin D_3; hyperuricemia, hypertriglyceridemia, insulin resistance. Bone changes (*renal osteodystrophy*) include *osteitis fibrosa cystica,* osteoporosis and rickets (children).

➢ Besides biochemical tests (blood urea, serum creatinine, serum electrolytes including levels of potassium, sodium, calcium and phosphate), ultrasonography is important for assessing kidney size. Presence *of small kidneys, bone disease, anemia and peripheral neuropathy* in a patient with renal failure *point to chronicity* of the disease. When CRF is associated with a normal size of the kidneys, consider polycystic kidney disease, diabetes, amyloid, malignant hypertension, and vasculitis.

➢ Treatment of CRF includes restriction of dietary protein and phosphates, control of hypertension (and diabetes mellitus, if present) avoiding dehydration, monitoring serum electrolytes, avoiding potassium-rich foods and nephrotoxic drugs, calcium supplementation with phosphate binders, and administering recombinant erythropoietin for anemia. Indications for dialysis are as for ARF. For patients with ESRD, consider dialysis and renal replacement therapy.

Dialysis and renal transplantation

➢ *Dialysis* is a procedure in which the patient's blood is perfused across a semipermeable membrane against a *dialysate* solution. The membrane may be synthetic (as in *hemodialysis*) or natural (*peritoneal dialysis*) and the procedure results in removal of sodium, water, potassium and low molecular weight solutes such as urea from blood.

➢ Dialysis may be required in the treatment of both acute and chronic renal failure complicated by water overload, acidosis, hyperkalemia and uremic symptoms. It may also be used for the treatment of certain cases of poisoning (e.g., aspirin, methanol).

➢ In patients with chronic renal failure, *chronic ambulatory peritoneal dialysis* may be an alternative to intermittent hemodialysis. While it has the advantage of not requiring a dialysis machine or a vascular access, peritonitis can be a troublesome complication.

➢ *Renal transplantation* is now accepted as a reasonable therapeutic option for patients with end stage renal disease.

  ➢ The donor kidney must be HLA and DR matched with the recipient to avoid *rejection* by the host. Preoperative blood transfusions reduce the risk of rejection.

  ➢ Immunosuppressive drugs (prednisolone, azathioprine and cyclosporine) are necessary to prevent rejection.

  ➢ The donor kidney is transplanted into the right iliac fossa of the recipient where it is more accessible for biopsy (to exclude rejection), if required.

14.5 Glomerular disorders

Glomerular disorders arise due to a complex interplay of several injurious mechanisms. These include vascular disturbances, coagulation disturbances and immune mechanisms of glomerular injury. Among these, the immune mechanisms are perhaps the most important and are discussed below.

Basic immune mechanisms of glomerular damage

Two basic mechanisms of glomerular injury are well-recognised. The less common mechanism is where the glomerular basement membrane (GBM) acts as an in situ antigen, and antibodies to this membrane are deposited, giving rise to a typical linear staining on immunofluorescence microscopy. The more common mechanism is where the kidneys are damaged by the deposition of antigen-antibody complexes which bear no immunochemical relationship to the glomerular structures. These complexes must be formed *in equivalence*[1] or *in slight antigen excess* in order to localise in glomeruli and appear lumpy on immunofluorescence microscopy (complexes formed in antibody excess are insoluble, those in marked antigen excess are too small to localise in kidneys). These complexes may contain IgG, IgA or IgM antibodies and may deposit in the mesangium, the subendothelial region or the subepithelial region. Why the immunoglobulin component and the site of deposition vary in different diseases is not clear. Each disease is, however, usually characterised by a specific site of deposition of immune complexes with a particular immunoglobulin component (Fig 14.20).

Part of the differences in clinical manifestation are accounted for by these variations. Deposits with IgG activate complement via the classical pathway whereas IgA deposits activate complement less effectively (via the alternate pathway). Deposits in the mesangium and subendothelial sites are accessible to inflammatory cells whereas deposits in the subepithelial surface are relatively inaccessible and damage the glomerulus by non-inflammatory mechanisms such as complement-mediated membranolysis. Thus, disorders with IgG deposits in the mesangium and subendothelium (for example, lupus nephritis) result in severe glomerular inflammation and an acute 'nephritic' presentation, with hematuria and oliguria. Disorders with IgA deposits in the mesangium result in a less dramatic presentation, usually as recurrent macroscopic hematuria (Berger's disease). In membranous nephropathy with subepithelial immune complex deposits, a non-inflammatory histology results in an insidious onset nephrotic syndrome. Exceptions to these generalisations are, however, only to be expected. Thus post-infectious glomerulonephritis has a nephritic presentation although the immune complex deposits are subepithelial. This may be due to a severe inflammation within the glomerulus in this disorder.

[1] Meaning equiproportional amount of antigen and antibody

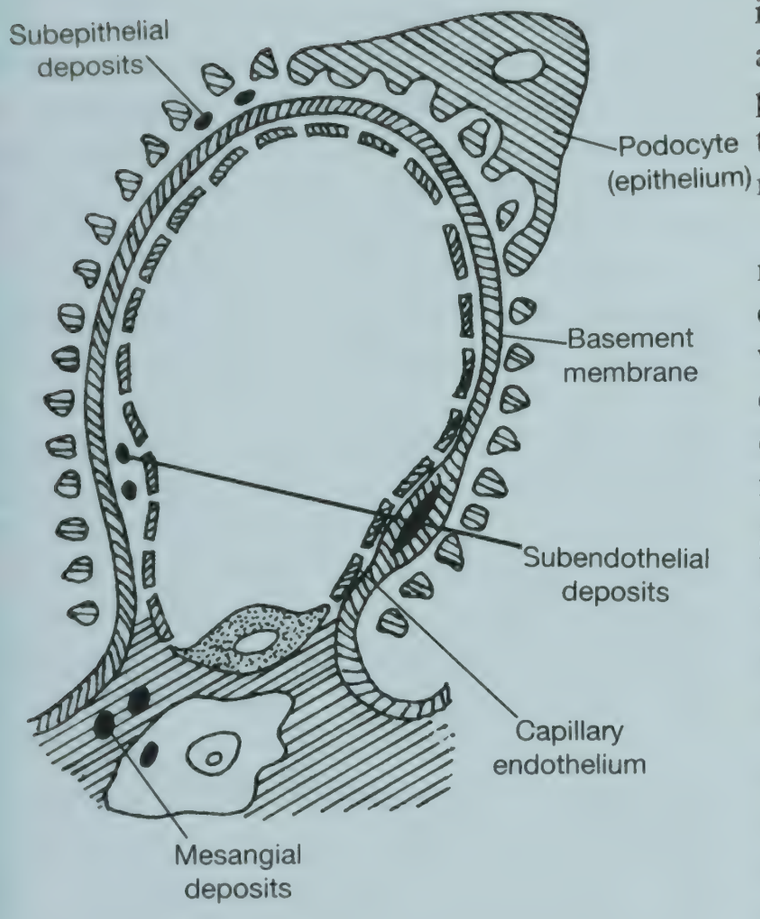


Fig 14.20 Deposition of immune complexes

Acute Glomerulonephritis

Acute glomerulonephritis is an acute inflammatory reaction within the glomerulus; its clinical counterpart is the acute nephritic syndrome: sudden onset of hematuria, oliguria and renal impairment.

Pathophysiology The three pathophysiologic hallmarks of acute glomerulonephritis are an altered glomerular filtration rate, an abnormal glomerular permeability and an altered renal handling of salt and water. The first accounts for oliguria, the second for hematuria and the last for edema and hypertension which completes the clinical profile of acute nephritis. A decrease in glomerular filtration is related to two processes. The marked glomerular hypercellularity involves the capillaries, and the capillary surface area for filtration is consequently reduced. Also, the proliferation of the epithelial cells in Bowman's space (resulting in varying degrees of crescent formation) causes a decline in the transglomerular hydrostatic pressure gradient (altered Starling's forces due to raised tissue hydrostatic pressure) thereby reducing glomerular filtration.

The altered permeability of the glomerulus may be related to mechanical disruption of the capillary wall (resulting in the leak of RBCs as well as causing hematuria) or disturbances in charge selectivity (loss of glomerular polyanion due to inflammation). Another recently recognised phenomenon is that in acute glomerulonephritis the glomerular pore size becomes heterogeneous or 'heteroporous' with the appearance of an abnormal population of enlarged pores. This abnormal permeability results in proteinuria as mentioned earlier.

The abnormal salt and water retention is also due to the interaction of several factors. A reduced filtered sodium load (due to a decrease in the glomerular filtration rate) results in avid tubular reabsorption of sodium. Sodium retention is by non-aldosterone-dependent mechanisms as plasma levels of renin and aldosterone are low; edema, fluid retention and volume-dependent hypertension result.

Renal Disorders with Acute Nephritic Presentation

Postinfectious glomerulonephritis

Postinfectious glomerulonephritis may be related to bacterial, viral, fungal, protozoal or helminthic disease. By far the commonest offending agent is group A β hemolytic streptococcus, the prototype for postinfectious glomerulonephritis.

Epidemiology The epidemiology of poststreptococcal glomerulonephritis is different in the tropics and the temperate zones. In the temperate zones, both sporadic and epidemic cases are associated with streptococcal

pharyngitis with a nephritogenic strain (usually M type 12). In the tropics, the sporadic cases may follow episodes of streptococcal pharyngitis but the epidemics are almost always associated with skin infection. The skin infection may be streptococcal impetigo or a superinfected scabies lesion. Poor hygiene and overcrowding are important contributory factors. While the pharyngeal nephritogenic strain is predominantly M type 12 streptococcus, several skin strains of streptococci can cause glomerulonephritis in the tropics.

The epidemics occur in school-going children in the summer and affect both sexes equally. A latent period of 20 days after the onset of skin infection is typically seen before the development of clinical nephritis. Sporadic cases affect adults, occur in the winter and are related to episodes of streptococcal pharyngitis. The latent period after the episode of pharyngeal infection is shorter and averages about 10 days. Men are affected twice as often as women.

Pathology Poststreptococcal glomerulonephritis is characterised by a diffuse proliferative glomerulonephritis with mesangial and endothelial hypercellularity, a polymorphonuclear leukocytic infiltrate and interstitial edema. Immunofluorescence reveals granular lumpy deposits of C3 and IgG, and electron microscopy identifies subepithelial electron dense humps. Epithelial cells in Bowman's space also proliferate resulting in focal crescent formation.

Clinical features and diagnosis The typical presentation with 'smoky' urine, hypertension and periorbital edema in a child, following a latent period of 10–20 days after a pharyngeal or skin infection, strongly suggests the diagnosis of poststreptococcal glomerulonephritis. Isolation of streptococcus from the throat or skin, demonstration of hypocomplementemia and elevated titres of antistreptococcal antibodies (anti-streptolysin O for pharyngeal infection, anti-hyaluronidase or anti-DNAase B antibodies for skin infection) are strong supporting evidence for the diagnosis. When the patient is an adult, when there is no latent period after infection (synpharyngitic nephritis) or if the serum complement levels are normal, an alternate diagnosis such as Ig A nephropathy or a rapidly progressive glomerulonephritis must be considered. Prolonged oliguria or anuria, nephrotic range proteinuria (>3.5 g/24 hour urine) or clinical evidence of a systemic disease are indications for a renal biopsy.

Prognosis Epidemic forms of the disease in children and adults have an excellent prognosis with recovery in more than 95 per cent of the patients. Sporadic forms in children or adults tend to be associated with extensive crescentic glomerulonephritis and progressive renal failure in 5–30 per cent of cases.

Treatment Treatment is largely supportive. Hypertension must be treated promptly, as children are prone to develop an encephalopathy or pulmonary edema with severe uncontrolled hypertension. Diuretics are required for edema resolution and a ten-day course of penicillin is indicated if throat or skin cultures yield streptococci. Penicillin prophylaxis is not indicated (unlike after an episode of acute rheumatic fever) since recurrences are very rare.

Rapidly progressive glomerulonephritis

Rapidly progressive glomerulonephritis is a clinical syndrome characterised by an acute 'nephritic' presentation in which the renal failure, instead of improving, progresses over weeks to months, to advanced renal failure.

Pathology and etiopathogenesis Histology reveals extensive, diffuse circumferential proliferation of the epithelial cells of Bowman's space, resulting in diffuse crescents which compress the glomerular capillaries, thereby interfering with renal function. The crescents

contain epithelial cells, mononuclear cells and fibrinogen-fibrin polymers. Fibrin is said to play a key role in initiating epithelial cell proliferation. The glomerular tuft itself usually shows only minimal changes.

Prominent endocapillary proliferation would suggest an infectious etiology (poststreptococcal glomerulonephritis complicated by crescent formation) while endocapillary necrosis would suggest an underlying systemic vasculitis.

Pathogenetically three subtypes of the disorder exist (see Table 14.2). About 20 per cent of cases have elevated serum antiglomerular basement membrane (anti-GBM) antibodies and on immunofluorescence linear deposition of IgG.

C3 is seen along the capillary wall. Serum complement levels tend to be normal. This entity is called 'anti-GBM' disease. When, in addition, the disorder is associated with hemoptysis, the triad – glomerulonephritis, pulmonary hemorrhage, anti-GBM antibody – is complete and the patient is said to have Goodpasture syndrome. These patients are frequently positive for HLA Drw2 antigen. These patients are young (<50 years) and are usually males (M:F=5:1). Patients with anti-GBM disease, without pulmonary hemorrhage, are older and both sexes are equally affected. About 40 per cent of cases are characterised by a lack of serum anti-GBM antibodies, presence of hypocomplementemia and a granular deposition of IgG, C3 on immunofluorescence microscopy of renal biopsy tissue. These patients have immune complex disease frequently secondary to a systemic disease such as systemic lupus erythematosus, Henoch schonlein purpura or cryoglobulinemia.

About 40 per cent of cases lack serum anti-GBM antibodies, have normal complement levels and in these immunofluorescence microscopy does not reveal any immune deposits. These *pauci*[1] *immune* patients are said to have idiopathic rapidly progressive glomerulonephritis and tend to be older (>50 years). The serological presence of *antineutrophil cytoplasmic antibodies* (ANCA) in some patients of this subset strongly suggests that they may be *forme fruste*[2] of systemic vasculitis. (These antineutrophil cytoplasmic antibodies are seen in Wegener's granulomatosis and systemic necrotising vasculitis).

Clinical features Crescentic glomerulonephritis presents as an abrupt onset of renal failure, with normal sized kidneys and frequently with normal blood pressure as well. At the time of presentation, more than half the patients are oliguric and azotemic. A history of hemoptysis antedating the nephrotic illness suggests the diagnosis of Goodpasture syndrome.

Course and prognosis Without definitive treatment, more than three-fourths of patients will require treatment for end stage renal disease at the end of one year. The subsets without antiglomerular antibodies seem to have a better prognosis.

Therapy The therapeutic measures have been targeted at removing circulating anti-GBM antibodies by plasma exchange, suppressing epithelial cell proliferation and immune inflammation with the use of steroids and cytotoxic agents, and inhibiting crescent formation with the use of anticoagulants (heparin or warfarin) and antithrombotic agents (dipyridamole).

Intensive plasma exchange (plasmapheresis) can be carried out three times a week. This therapy is also useful, surprisingly, in the pauci immune subsets which do not have anti-GBM antibodies. However, this therapeutic modality is expensive and carries a risk of bleeding and infection.

Steroid therapy is usually administered as a *pulse* (single large dose) of methyl prednisolone,

[1] 'Pauci' means few, small or less.

[2] 'Forme fruste' means a partially expressed form of the disease.

usually 30 mg/kg, given intravenously over half an hour either daily or on alternate days. Therapeutic success rates have been about 70 per cent with either mode of therapy. Alkylating immunosuppressive agents have also been combined with steroids with variable degrees of success and their exact status in the treatment of crescentic glomerulonephritis may be clearer in the coming years. Probably, the histopathologic evidence of 'necrotising', glomerular lesions may be taken as indicative of a likely response to these drugs. Similarly, anticoagulant use has not been evaluated properly in large scale trials.

They would, however, be contraindicated in the presence of pulmonary hemorrhage or advanced renal failure. All four agents (steroid + cytotoxic agent + anticoagulant + antithrombotic) are sometimes tried as *quadruple therapy.*

It should be emphasised that the response to any therapeutic regimen is likely to be good early in the disease and likely to be disappointing in the burnt-out phases of the disease. Hence an early diagnosis of the condition is a must.

The Nephrotic Syndrome

The nephrotic syndrome is a clinical syndrome characterised by albuminuria (>3.5 g/1.73 m^2/day or >40 mg/m^2/hour), hypoalbuminemia, edema and hyperlipidemia.

Pathophysiology The common denominator is the damage to the glomerular filtration barrier. This damage may result in a loss of net negative charge on the glomerular capillary wall due to loss of the anionic sialoglycoproteins (called glomerular polyanion). It may also be due structural defects of the basement membrane, damaged either by immune or by non-immune mechanisms. This abnormally 'leaky' filtration barrier results in proteinuria, predominantly an albuminuria. Since there is urinary loss of albumin, at a rate exceeding the daily rate of hepatic synthesis of albumin, serum albumin levels fall. A reduction in serum albumin results in a fall in plasma oncotic pressure in all the tissues. There is a change in Starling's forces because of this fall in plasma oncotic pressure, relative to the capillary hydrostatic pressure; this results in fluid leaving the capillaries in areas of low tissue pressure, like the periorbital region. There is a reduction in effective plasma volume which activates the renin–angiotensin system, stimulates the sympathetic nervous system and antidiuretic hormone release. All this results in aldosterone and vasopressin-dependent salt and water retention. The reduced plasma oncotic pressure and urinary loss of regulatory apoproteins step up hepatic lipoprotein synthesis, resulting in hyperlipemia. All lipid components seem to increase (triglycerides, cholesterol and chylomicrons). The elevated

Table 14.2 Immunologic subsets of rapidly progressive glomerulonephritis

Subset	*IF on renal biopsy*	*Serum complement levels*	*Serum anti-GBM antibody*
Goodpasture syndrome /Anti-GBM disease	Linear	Normal	++
Immune complex disease	Lumpy-bumpy (granular)	Decreased	Absent
Idiopathic	Nil	Normal	Absent

IF = immunofluorescence; GBM = glomerular basement membrane

ipid components also leak through a defective iltration barrier (lipiduria) and result in 'oval atty bodies' in the urine.

The loss of antithrombin III (a circulating nticoagulant) and elevated levels of fibrinogen esult in a hypercoagulable state. Urinary losses of transferrin, vitamin D binding protein and IgG result in anemia, osteomalacia and a susceptibility to infections, respectively.

Etiopathogensis and epidemiology The etiological spectrum of the nephrotic syndrome in the tropics differs from that in the non-tropical areas. This is related to the high rate of various infections and malnutrition. Protein energy malnutrition results in lower levels of serum proteins and, therefore, an earlier onset of edema. Parasitic infections are a common cause of the nephrotic syndrome in several areas. Thus *Plasmodium malariae* infection is a leading cause of the nephrotic syndrome in certain parts of Africa like Nigeria and Uganda. There are other areas of Africa where, despite the endemicity of malaria, quartan malarial nephropathy is rare. This raises the posssibility that only some strains of *P. malariae* are nephritogenic. Similarly, glomerular involvement with schistosomiasis results occasionally in the nephrotic syndrome.

Overall in north India, over 80 per cent of the cases of nephrotic syndrome are related to primary glomerular disease. Of these, measangioproliferative glomerulonephritis is the commonest (30 per cent). Minimal change disease (15 per cent), membranous nephropathy (20 per cent) and focal glomerulosclerosis (10 per cent) are other important conditions that result in the nephrotic syndrome. In south India, minimal change disease is twice as common as in north India. Twenty per cent cases of nephrotic syndrome are related to secondary glomerulopathies. Diabetes, amyloidosis, and systemic lupus erythematosus are important causes in this category.

General principles of treatment Treatment includes judicious use of diuretics to reduce edema (without aggravating hypovolemia) and an adequate dietary intake of proteins. High protein diets are probably not useful as they only serve to increase urinary protein loss. Specific treatment will depend on the particular glomerular histology.

Disease with a Nephrotic Presentation

Minimal change disease

Incidence Minimal change disease is the commonest cause of the nephrotic syndrome in children. In adults, too, it is a common cause of the nephrotic syndrome, being second in frequency after mesangioproliferative glomerulonephritis.

Pathogenesis Due to as yet unidentified factors, the glomerular polyanion is lost and a selective proteinuria results. Because of the remission of the disease after viral infections (measles) and its occurrence in subjects with pre-existing Hodgkin's disease, a T cell-mediated response has been implicated in the pathogenesis. HLA B12 is more prevalent in a subject with this disease.

Pathology Histology reveals a normal appearance under light microscopy and immunofluorescence microscopy, apart from a mild mesangial prominence. Electron microscopy reveals effacement of the foot processes of the podocytes, an appearance seen in other proteinuric states as well.

Clinical features The subject is typically a male child in the school-going age group. The blood pressure tends to be normal, the urinary sediment 'benign' and renal function preserved.

Treatment In a child with the nephrotic syndrome, if proteinuria is selective, a minimal change lesion is the most likely underlying renal histology; a biopsy is not required. Adults with this presentation, however, should have a kidney biopsy to determine the exact renal histology as

other causes of the nephrotic syndrome are also common.

Oral steroids (prednisolone 1–2 mg/kg/day) for 4–8 weeks results in remission in 90 per cent of children and 70 per cent of adults. Remission is defined as cessation of proteinuria (<300 mg/24 hours urine) for at least eight weeks. A partial response (defined as >300 mg to 1 g urinary proteins/24 hours) may also occur. Failure to reduce the 24-hour urinary protein excretion below one gram is labelled as treatment failure. Of the steroid responders, approximately 50 per cent develop relapses. Most relapses in children seem to be steroid responsive. Some patients become steroid dependent, requiring a low maintenance dose (5–10 mg/day).

Steroid failures, frequent relapses or 'steroid dependence' with steroid-induced side effects may require treatment with a brief 8–10 week course of a cytotoxic agent. Chlorambucil (0.1–0.2 mg/kg per day) seems to lead to longer and more stable remissions than cyclophosphamide (given in doses of 2–3 mg/kg/day). Cyclophosphamide (in higher doses of 4–6 mg/kg/day) has also been shown to induce lasting remissions. It may be used when other agents fail to induce remission. These remission-inducing modalities carry the risks of bone marrow depression, teratogeny and development of a lymphoid malignancy.

Prognosis The prognosis is excellent, with ten-year survival exceeding 90 per cent.

Mesangial proliferative glomerulonephritis

Mesangial proliferative glomerulonephritis represents a heterogeneous group of disorders characterised by a diffuse increase in the number of mesangial cells and in a mesangial matrix. The glomerular basement membrane, the capillary endothelium and the epithelium lining Bowman's space are all normal.

Immunofluorescence microscopy may reveal IgA, IgM or IgG deposits or, occasionally no immunoglobulin deposits. The subset with IgA mesangial deposits represents a form of IgA nephropathy (Berger's disease). The subset with IgG deposits is likely to be steroid-responsive whereas the subset with IgM deposits (so-called IgM nephropathy) is steroid resistant and progresses to focal segmental glomerulosclerosis.

Clinical features These may range from asymptomatic proteinuria or hematuria to frank nephrotic syndrome. Prominent loin pain suggests Berger's disease. A third of patients are hypertensive and a similar number have reduced creatinine clearance at presentation.

Therapy and prognosis As the entity includes a heterogeneous group of disorders, the prognosis is variable and the natural history not very well delineated. Steroid-unresponsive patients are at risk of developing end stage renal disease.

Membranous glomerulopathy

Incidence Although it is rare in children, it is a common cause of the nephrotic syndrome in adults.

Etiology Although it is most often a primary glomerular disorder, membranous nephropathy may on occasion be secondary to infections (hepatitis B, syphilis, quartan malaria), collagen vascular disease (systemic lupus erythematosus) or drug therapy (notably d-penicillamine, captopril, gold). Rarely, it may be associated with visceral malignacies, usually solid tumours such as lung or colonic cancers. An association with HLA DRw3 has also been noted.

Pathology Early in the disease, light microscopic appearance of the glomerulus is normal but electron microscopy reveals subepithelial electron dense immune deposits. As the disease progress, basement membrane thickening (best seen with a silver impregnation stain) appears. Spike-like projections of the basement membrane encircle the immune deposits, giving rise to a *spike and dome* appearance.

Clinical features A nephrotic syndrome with normal blood pressure, a 'benign' urinary sediment and preserved renal function is a commonest presentation. The clinical picture may be, therefore, indistinguishable from minimal change disease, apart from the onset in adulthood. Renal vein thrombosis is a frequent complication; it is suggested by a rapid decline in renal function in a stable patient.

Laboratory features Complement levels tend to be normal. A routine check for hepatitis B antigen, VDRL test and antinuclear antibodies (ANA) must be carried out in every patient to rule out a secondary cause of membranous nephropathy.

Prognosis and treatment Roughly a third of the patients have lasting spontaneous remissions. Another third develop variable degrees of proteinuria with mild azotemia and a third develop end stage renal disease over a 5–10 year period.

Therapy with glucocorticoids has yielded variable results. Nevertheless, a short course of steroids is worth a trial. Adverse prognostic factors include onset at a later age, presence of hypertension, massive proteinuria and biopsy evidence of marked basement membrane thickening with tubular atrophy. Presence of renal impairment has been taken by some physicians as an indication for cytotoxic drug therapy but the issue is still far from settled.

Focal glomerulosclerosis

Incidence Focal glomerulosclerosis is the most common cause of steroid resistant nephrotic syndrome in children. It is also a common cause of the nephrotic syndrome in adults accounting for 10 per cent of cases in an Indian series.

Pathology and etiopathogenesis The hallmark is *sclerosis* and hyalinisation of some glomeruli *(focal)*, and within an affected glomerulus only some capillary tufts are affected *(segmental)*. Juxtamedullary glomeruli seem to be preferentially involved and other associated features include a mild mesangial prominence, collapse of capillary loops, adhesions of the sclerosed portions of the glomerulus to Bowman's capsule and prominent tubulo-interstitial damage. Immunofluorescence reveals IgM and C3 deposits in the sclerotic lesions. It has been hypothesised that the initiating event may be the defective contractile function of the mesangial cells which results in glomerular vasodilatation, consequent intraglomerular hypertension and a secondary sclerosis of the capillaries. Secondary causes of focal glomerulosclerosis include heroin abuse, chronic vesico-ureteric reflux and the acquired immune deficiency syndrome (AIDS).

Clinical features The commonest presentation is like the nephrotic syndrome but, unlike membranous nephropathy or minimal change disease, the urine sediment is not benign (hematuria is common), hypertension may occur and the glomerular filtration rate is impaired. Proteinuria tends to be non-selective.

Prognosis and treatment Prognosis is related to the degree of proteinuria. About 50 per cent of patients with 'nephrotic range' proteinuria progress to end stage renal disease in 10 years whereas 80 per cent of patients with 'non-nephrotic proteinuria'[1] retain normal renal function over the same period. Since roughly a third of the patients may be steroid-responsive, a trial of steroids is indicated.

Membranoproliferative glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) is a proliferative glomerulonephritis associated with hypocomplementemia and a characteristic histologic picture of lobular appearance of the glomerular tuft and a double contour of the capillary walls (hence also called *lobular* or *mesangiocapillary* glomerulo-

[1] Refers to less than 3.5 g protein/24 hours urine

nephritis). It is, therefore, a pathologic diagnosis (like most primary glomerulopathies).

Pathology and etiopathogenesis Two subsets have been described in this entity. Type I MPGN is an immune complex disease in which granular subendothelial immune deposits activate the classical complement pathway. Light microscopy reveals mesangial hypercellularity. The mesangial matrix has extensions which gradually interpose between the glomerular basement membrane and the capillary endothelium — a phenomenon called *circumferential mesangial interposition.* This incorporation of the mesangial matrix into the thickened capillary wall results in a 'double contour' or *tram track* appearance. The immune deposits contain IgG and C3. The disorder may be secondary to chronic hepatitis B antigenemia or systemic lupus erythematosus.

Type II MPGN has a renal histology like Type I MPGN but the glomerular basement membrane itself is thickened and has electron dense deposits, hence the name *dense deposit disease.* There is a greater incidence of epithelial cell crescent formation. The immunoglobulin component in the deposits is usually IgM. The disorder seems to be mediated by persistent complement activation, probably by the alternate pathway. The serum of the patients has a factor referred to as the *C3 nephritic factor.* The C3 nephritic factor is actually an auto-antibody to C3 convertase, one of the key enzymes in the alternate complement pathway. It stabilises C3 convertase, that is, it protects the enzyme from its endogenous inactivator, so that the C3 convertase–C3 nephritic factor complex results in persistent complement activation, and therefore complement-mediated damage of the glomerulus occurs.

Clinical features Membranoproliferative glomerulonephritis affects the young (age group 7–35 years). Nephrotic syndrome with associated hypertension, an 'active' urine sediment and renal impairment are the commonest presenting features. Hypocomplementemia is usually seen. Episodes of acute nephritis may also occur.

Prognosis and treatment Type II MPGN has a worse prognosis than Type I with a tendency towards frequent nephritic episodes. Roughly half the patients have end stage renal disease in ten years.

Unlike other glomerulopathies, Type I MPGN seems to respond to antiplatelet drug therapy (a combination of aspirin and dipyridamole). Steroids have also been used in both forms of the disease with some benefit. Type II MPGN recurs in the transplanted kidney.

Glomerular Disorders Presenting as Recurrent Hematuria

IgA nephropathy (Berger's disease)

A nephropathy is a primary glomerulonephritis wherein immunofluorescence microscopy shows IgA deposits, usually in the mesangial areas. There is no characteristic feature on light or electron microscopy. Some systemic disorders (liver disease, SLE, Henoch-Schonlein purpura and leprosy) may result in an identical renal picture and must therefore be excluded before the diagnosis of 'idiopathic IgA nephropathy' (Berger's disease) is made.

Incidence Whenever it is looked for (in centres with facilities for immune microscopy), IgA nephropathy is found to be common. In India, around 5–6 per cent of all kidney biopsies show IgA nephropathy. Worldwide, the incidence is highest in Japan (30 per cent).

Pathogenesis IgA nephropathy is a single organ manifestation of a systemic disorder. The currently accepted theory of etiopathogenesis is outlined below. A defect in mucosal immunity, permits an exogenous antigen (viral or dietary) to enter the body. In response, there is

polyclonal[1] increased production of IgA resulting in intermediate sized, IgA containing circulating immune complexes. Such complexes would usually be cleared in the liver or mononuclear-phagocytic system. A defect in these non-renal clearance mechanisms contributes to renal mesangial deposition of the IgA-antigen complex in a granular, diffuse pattern.

It is important to realise that IgA deposits are necessary but not sufficient to cause IgA nephropathy. Such deposits may occur transiently after a viral infection, without any evidence of renal damage. However, in susceptible individuals (there is an association with HLA B35 and DR4), the IgA deposits activate complement (via the alternate pathway), stimulate the mesangial cells to secrete proteases and activate macrophages, thus damaging the nephrons.

Pathology The light microscopic picture ranges from normal (five per cent) to diffuse thickening of the measangium with foci of mesangiolysis (60 per cent). Focal, segmental glomerular sclerosis and crescents indicate a poor prognosis. Tubular atrophy, interstitial fibrosis and arteriolar sclerosis all worsen the prognosis. The mesangial deposits are fuchsinophilic (red staining on Masson's trichrome stain). Skin biopsy shows IgA deposits in 50 per cent.

Clinical features IgA nephropathy is seen typically in young adults with a M:F ratio of 3:1. Hematuria is seen in all patients. It may remain microscopic and persistent, or consist of recurrent episodes of macroscopic hematuria (often precipitated by viral infections, alcohol or exercise). Surpisingly, the group with microscopic hematuria runs a greater risk of progression to end stage renal disease. Selective proteinuria (1 g/day) occurs in three-fourths, hypertension in half, acute renal failure in a tenth and progression to end stage renal disease in a fourth.

[1] Polyclonal means that the increased IgA consists of antibodies against several antigens.

Treatment Control of hypertension may delay the onset of end stage renal disease. Management is as in other primary glomerulonephritides. Mesangial IgA deposits may recur in a transplanted kidney.

Renal Involvement in Systemic Diseases (Table 14.3)

Systemic lupus erythematosus

Pathologic involvement of the kidneys is almost universal in this disease. The type of pathology is, however, variable and the classification with clinical presentation is outlined in Table 14.4.

Course and prognosis As in the primary glomerulopathies, histologic classes I and II have an excellent prognosis and class IV the worst prognosis. Prognosis for histologic classes III and V is intermediate.

Treatment Class I and II renal lesions do not require any treatment. Membranous lupus nephritis is best treated with steroids. Treatment of class III and IV lesions is guided by biopsy features of activity and chronicity. The signs of acitivity include glomerular hypercellularity, necrosis and cellular crescents whereas fibrous crescents, sclerotic glomeruli and interstitial fibrosis indicate chronicity. Patients with highly active biopsy features and few chronic features are those who require aggressive immunosuppression. Those patients with predominating 'chronic' features in biopsy do not merit cytotoxic drug therapy. Since clinical differentiation between the various subsets of lupus nephritis is difficult, the presence of significant urinary abnormalities strongly demands the performance of a renal biopsy so that therapy can be targeted at preventing progressive renal damage.

The therapeutic options for immunosuppression include oral azathioprine or cyclophosphamide (2 mg/kg/day of either agent), a combination of the two, intravenous cyclophosphamide (1 g/m^2 i.v. every month) or

Table 14.3 Renal involvement in systemic disease

Disease	*Incidence of renal involvement*	*Renal pathology*	*Clinical presentation*
Classical polyarteritis nodosa	90%	• ischemic glomerulopathy • crescentic GN*	• renal failure • hematuria
Wegener's granulomatosis	70%	• focal proliferative GN*	• hematuria • proteinuria
Progressive systemic sclerosis	50%	• vascular hyperplasia • fibrinoid vascular necrosis	• renal failure
Sjogren syndrome	40%	• interstitial nephritis	• asymptomatic • renal tubular acidosis
Essential mixed cryoglobulinemia	40%	• diffuse proliferative GN*	• hematuria • acute nephritic syndrome • renal failure
Thrombotic microangiopathy (TTP/HUS)*	60%	• glomerular microangiopathy	• renal failure
Multiple myeloma	50%	• amyloid • tubular obstruction • cast nephropathy	• nephrotic syndrome • renal failure
Amyloidosis	70%	• amyloid deposit	• nephrotic syndrome • renal failure

* GN = glomerulonephritis, TTP = thrombotic thrombocytopenic purpura, HUS = hemolytic-uremic syndrome

pulse methyl prednisolone (30 mg/kg every month). Pulse doses of steroids seem to be more effective than high oral doses of steroids. It has been shown that this may be related to a more sustained inhibition of complement activation and a congealing of membranes (rapid rigidification) in the inflammatory cell which inhibits the release of various mediators of inflammation. This congealing is secondary to incorporation of the steroid within the fluid 'lipid bilayer' cell membrane.

Diabetic nephropathy

Renal disease in diabetics ranges from glomerulopathy, tubular dysfunction, a propensity for urinary tract infection and papillary necrosis, to bladder dysfunction secondary to diabetic autonomic neuropathy.

Table 14.4 Lupus nephritis

Class	*Frequency*	*Clinical presentation**
I (normal)	< 5%	no symptoms or signs of renal disease
II (minimal or mesangial lupus nephritis)	~ 15%	asymptomatic proteinuria
III (focal proliferative GN)	~ 20%	asymptomatic proteinuria
IV (diffuse proliferative GN)	~ 50%	nephrotic syndrome with renal impairment
V (membranous GN)	~ 20%	nephrotic syndrome without renal impairment

* Overlap in clinical manifestations of different histologic classes is not uncommon.

Only diabetic glomerulopathy is discussed in detail in this section.

Incidence Upto 50 per cent of insulin-dependent diabetes mellitus patients develop renal disease if the duration of diabetes is more than 20 years.

Pathogenesis, stages and pathology The first stage of diabetic nephropathy involves altered vasoregulatory tone of the renalvessels. The afferent and efferent arterioles dilate with consequent glomerular hyperfiltration, that is, elevation of the glomerular filtration rate. This change in renal vascular tone has been linked to hyperglycemia and the elevated levels of hormones such as glucagon and growth hormone which are seen in early diabetes mellitus. The kidneys appear normal histopathologically, although the gross size may be increased. The clinical counterpart of hyperfiltration is an increase in the glomerular filtration of albumin. This *microalbuminuria* is, however, less than 100 µg/minute (but more than the normal levels of 15 µg/minute), so that it is below the threshold for detection by conventional tests for urinary protein.

The next stage of diabetic glomerulopathy is characterised by *macroproteinuria* (proteinuria of a greater magnitude), easily detected by conventional tests. Ultrastructurally, the mesangium undergoes an expansion in its collagenous components, and the glomerular basement membrane thickens. Although this is commonly a diffuse glomerulosclerosis, occasionally the accumulation of mesangial matrix is more nodular, when it is described as nodular glomerulosclerosis (also called the *Kimmelstiel-Wilson* nephropathy).

The third stage is one of advanced diabetic nephropathy with a decline of glomerular filtration at a rate of 1 ml/minute/month. Azotemia, hypertension and edema become manifest.

Treatment There is no definitive treatment. Vigorous control of the diabetes does seem to *prevent* nephropathy. Angiotensin-converting enzyme inhibitors like captopril have shown some promise in the initial trials by preventing glomerular hyperfiltration. Hypertension must be treated and the azotemic patient will require evaluation for renal replacement therapy.

KEY CONCEPTS

Acute glomerulonephritis

- AGN is characterised by the acute onset of smoky, *cola-coloured urine,* azotemia, peripheral edema and hypertension. Usually AGN occurs about 10–20 days after an episode of streptococcal infection (impetigo or pharyngitis).
- Urinalysis reveals hematuria (red cell casts) with mild proteinuria. ASLO may be elevated. Renal biopsy reveals hypercellular glomeruli infiltrated by PMN, eosinophils, monocytes and *large dense subepithelial* immune-complex deposits containing IgG, C3.
- Prognosis is a good in the majority of children. However, about 30% of adults with AGN experience progressive derangement of renal function of variable degree. Treatment measures include reduction of dietary sodium, control of hypertension and edema, mild protein restriction (if azotemia is present), and administration of antibiotics if there is evidence of active streptococcal infection. Immunosuppressive agents or steroids have no role in the management of AGN.

Rapidly progressive glomerulonephritis

- RPGN is a renal response to diverse conditions which is characterised by clinical evidence of a rapid loss of renal function and by *histologic* evidence of *epithelial cell proliferation* and *crescent formation.*
- About a third of the cases are related to the serologic presence of anti-GBM antibodies (Goodpasture syndrome; *linear* deposits; normal serum C3 levels), another third are due to immune complexes (SLE, Henoch-Schonlein purpura, infections; *granular* deposits, reduced serum C3 levels), while the rest are pauci immune (systemic vasculitis; *antineutrophil cytoplasmic antibodies*; serum C3 is normal).
- The clinical hallmark of RPGN is onset of hematuria, mild proteinuria and oliguria. Variable degrees of edema may be present. Some patients manifest hypertension. A definite diagnosis of RPGN requires a renal biopsy.
- Treatment of RPGN depends on the renal histology. Aggressive control of hypertension is recommended. Anti-GBM disease is best treated with a combination of plasmapheresis, prednisolone and cytotoxic agents. Immune complex disease is managed with pulse doses of glucocorticoids combined with cytotoxic agents.
- More than 50% of RPGN patients progress to renal failure over 2 years. Age >60 years and >70% crescents in glomeruli on examination of renal biopsy portend an adverse prognosis. RPGN which is pauci-immune or which is secondary to systemic disease has a better prognosis.

Nephrotic syndrome

- A diagnosis of NS is considered if the following *quartet* is present: *proteinuria* (>2g/m^2/day), hypoalbuminemia (<3 g/dl), *edema* and *hyperlipidemia.* NS is associated with a *hypercoagulable state* (renal vein thrombosis is one manifestation) and an increased susceptibility to infections.
- NS may be *primary* (idiopathic; minimal change disease in 80% of children; membranous glomerulonephritis in 30–50% of adults) or *secondary* to systemic disease (diabetes mellitus, SLE, HIV infection, quartan malaria, drugs, neoplasms).
- Proteinuria may be *selective* (for albumin, as in minimal change disease) or *non-selective.* Measurement of 24-hour urine protein excretion is important. A definitive diagnosis of the underlying glomerulopathy requires a renal biopsy, although routine renal biopsy is not needed in most children. Serum levels of C3, C4 and ANA (to exclude systemic disease) may be estimated.
- Treatment of NS includes administration of a high protein diet in a non-azotemic patient; protein restriction is advisable in azotemic patiens. Avoid excess diuresis. Specific treatment (consisting of corticosteroids with or without cytotoxic agents) is based on the specific renal histology (except in children who are empirically treated with steroids initially).

Minimal change disease

- MCD is the most common cause of the nephrotic syndrome in children. It is associated with atopy, Hodgkin's disease, recent immunisation and HLA B12.
- No specific glomerular changes are seen on light microscopy; EM examination of renal biopsy reveals *fusion of the foot processes* of podocytes.
- Clinical presentation is as a nephrotic syndrome with *selective proteinuria*, normal blood pressure, a benign urine sediment and with normal serum C3 levels.
- Eighty per cent of patients are steroid-responsive, although relapses are frequent. Cytotoxic agents may be tried in steroid-resistant or steroid-dependent patients.

Mesangioproliferative glomerulonephritis

- Presentation is with non-selective proteinuria, hematuria, and normal serum C3 levels.

- There is histologic evidence of an increase in mesangial cells in the matrix; IgM IgG, C3 are deposited. If there are IgA mesangial deposits, *Berger's disease* must be suspected.
- This condition is usually non-responsive to steroids; cytotoxic agents are usually ineffective. About twenty per cent of patients progress to renal failure.

Membranous glomerulonephritis

- This is one of the common causes of nephrotic syndrome in adults. Men are affected twice as often as women. The condition may be *primary* (idiopathic) or *secondary;* secondary causes include connective tissue disease (SLE), infections (malaria, hepatitis B, syphilis), drugs (penicillamine), heavy metals and solid tumours.
- The histologic characteristics include a thickened glomerular basement membrane (*spikes*), granular subepithelial deposits of IgG, and foot process effacement. Serum C3 levels are normal.
- A definitive diagnosis requires renal biopsy. In every case it is important to search for and exclude a secondary cause. Treatment consists of antihypertensive drugs, and prednisolone alternating with chlorambucil. 25% of patients go into clinical remission while another 30% progress to renal failure. Male sex and old age are adverse prognostic factors.

Focal glomerulosclerosis

- FGS presents clinically with non-selective proteinuria, hypertension, hematuria, and renal failure of variable degree (50%); serum C3 levels are normal. There is an association with heroin abuse, vesico-ureteric reflux, AIDS and renal transplant rejection.
- The histologic hallmark is a focal and segmental involvement of glomeruli with deposition of IgM and C3 in a nodular fashion; atrophy of some glomeruli (sclerosis) is an additional feature.
- About twenty per cent of patients are steroid-responsive. Regimens which include prednisolone (with or without cytotoxic agents) are used.

Membranoproliferative glomerulonephritis

- MPGN represents a renal response to diverse stimuli which is characterised by proliferation of mesangium, formation of glomerular crescents, and reduction in serum C3 levels.
- Two types have been described. *Type I* (subendothelial deposits of IgG and C3; classical complement pathway activation) is associated with malaria, hepatitis B, SLE, hemolytic-uremic syndrome. *Type II* (intramembranous dense deposits of IgM and C3; alternate pathway activation) is associated with partial lipodystrophy.
- The clinical presentation of the two types is indistinguishable; a third of the subjects present with a nephritic illness, another third with nephrotic syndrome, the rest present with hematuria-proteinuria of variable degree.
- Type I MPGN is treated with a combination of dipyridamole and aspirin. High dose glucocorticoids and cyclosporin may be beneficial. Progression to renal failure is observed in 50 per cent of patients over a period of ten years.

14.6 Disorders of the renal tubules

Adult Polycystic Disease of the Kidneys

Polycystic kidney disease is an inherited disorder, characterised by cyst development and cyst growth in both the kidneys.

Heredity Polycystic kidney disease is an autosomally dominant condition with almost 100 per cent penetrance by the age of eighty. This means that if an individual with the disease survives to the age of eighty years, there is a near certainty that his kidneys will be cystic. The inheritance seems to be linked to the hemoglobin gene and the phosphoglycerate kinase gene on the short arm of chromosome 16.

Pathology and pathogenesis Although several theories have been propounded to explain the development of cysts in this disorder, the most accepted theory is that the renal tubular cells have an abnormal growth, and also an abnormally split basement membrane. The gross pathology of the kidneys reveals multiple cortical and medullary cysts with clear or serosanguineous fluid. The disorder seems to follow a sequential pattern: *discomfort* (flank pain) → *deformity* (nephromegaly) → *destruction* (renal failure). Cysts may occur in other organs, notably the liver, pancreas and the ovary. Hepatic cysts, present in a third of the patients, tend to be asymptomatic. Other visceral abnormalities of a non-cystic nature also occur. These include colonic diverticulosis in about two-thirds, myxomatous cardiac valvular degeneration in a third and intracranial 'berry' aneurysms in a tenth of the patients.

Clinical features Renal cysts are prone to bleed, become infected and enlarge. Flank pain and hematuria are common presenting features. There may be associated urinary tract infections and superimposed calculus disease as well. The kidneys are frequently palpable clinically. When the growth of the cysts interferes with renal parenchymal function, hypertension and nocturia become apparent. Eventually, a slowly progressive chronic renal failure sets in, usually above the age of fifty years. It is, however, not uncommon to see asymptomatic patients (even among the elderly) with preserved renal function.

Diagnosis Ultrasonography is the investigation of choice. The presence of extrarenal cysts (especially hepatic) in the patient or the presence of renal cysts in other family members differentiates adult polycystic kidney disease from multicystic renal disease (multiple simple cysts).

Treatment This is aimed at early recognition and treatment of the complications (which are bleeding, infections, hypertension and renal failure). Anemia and fluid overload are less common problems in the renal insufficiency which occurs secondary to this disorder, due to the preservation of erythropoietin secretion and the presence of tubular salt wasting.

Renal Tubular Acidosis

Renal tubular acidosis is a group of disorders characterised by metabolic acidosis consequent to a disordered acid-base handling by the kidneys (Table 14.5).

Table 14.5 Classification of renal tubular acidosis

Type		*Serum potassium*	*Urine pH*
I	(distal)	Hypokalemia	>5.5
II	(proximal)	Hypokalemia	<5.5
IV	–	Hyperkalemia	<5.5
III	(proximal+ distal)	Hypokalemia	–

Pathophysiology Renal tubular acid-base regulation involves two important steps: 1) bicarbonate reabsorption by the proximal tubules, and 2) excretion of fixed acid (100 meq/day) by the distal tubules. These two mechanisms differ inherently. At the proximal tubules, the bicarbonate reabsorption is closely coupled with reabsorption of sodium and equimolar secretion of H^+ ions (sodium-potassium ATPase dependent). Hence no transcellular pH gradient is established at the level of the proximal tubules. Further, the enzyme carbonic anhydrase is present intraluminally in the proximal tubules. At the distal tubules[1] a proton pump secretes H^+ ions into the lumen. Since this is not linked to sodium reabsorption, a pH gradient can be generated at this level. The sodium reabsorption at this level creates a negative lumen. This gradient favours intraluminal secretion of K^+ or H^+ ions. Sodium reabsorption at this level is through a channel which is stimulated by aldosterone. There is no intraluminal carbonic anhydrase at the distal tubules. This being the basic renal tubular physiology, let us see what goes wrong in the various forms of renal tubular acidosis (RTA) (Fig 14.21).

In proximal (Type II) RTA there is a failure to reabsorb urinary bicarbonate. Normally more than 85–90 per cent of the filtered bicarbonate is reabsorbed at this level, that is, the fractional excretion of bicarbonate is less than 15 per cent. Due to failure of $Na^+ - H^+$ exchange or defective carbonic anhydrase, bicarbonaturia occurs. The urine becomes alkaline and serum bicarbonate falls commensurately, resulting in a metabolic acidosis. The lowered renal tubule threshold for bicarbonate reabsorption is about 20 mEq/L, so that at a serum bicarbonate level of 20 mEq/L, bicarbonaturia ceases and urine pH falls again. However, the basic abnormality persists and is unmasked by a bicarbonate load (oral or intravenous) following which the bicarbonaturia begins and urine pH becomes alkaline. Since bicarbonate lost in urine in this disorder is partly lost as a potassium salt, hypokalemia is an important concomitant of proximal RTA. Since, the distal acidification mechanisms are intact, these patients can produce an acid urine and can excrete an acid load normally. This disorder is very rare in adults.

In distal tubular acidosis (Type I RTA — more appropriately called distal 'nephron' acidosis), the proton secreting pumps are deficient and the intraluminal pH cannot be lowered by the normal 2–3 pH units. Acid excretion is therefore subnormal and a metabolic acidosis results. This acidosis is associated with hypokalemia (as in Type II RTA). The sodium reabsorption at the distal tubules is compensated by potassium loss since no proton secretion is available for competition. The acidosis in both the proximal and distal types is 'hyperchloremic'; plasma chloride is high as there is no retention of phosphates, urates and sulphates, glomerular function being normal. However, urinary citrate is reduced only in distal RTA *(hypocitraturia)* as citric acid is not needed to buffer the lowered proton excretion. Normally, citrate chelates calcium, keeping it in

[1] Actually urinary acidification is a function of the whole distal nephron including the collecting ducts.

solution. Reduced chelation of calcium results in nephrocalcinosis and renal calculus disease in distal RTA.

Type IV RTA is associated with diminished sodium reabsorption due to deficient aldosterone production or action. Potassium and hydrogen secretion at the distal tubules is, therefore, disrupted. The result is renal salt wasting, subnormal net acid and potassium excretion. Hence, metabolic acidosis with hyperkalemia is seen in this disease. This is seen in diabetic nephropathy and other tubointerstitial nephropathies associated with decreased renal production of renin and consequent hypoaldosteronism *(hyporeninemic hypoaldosteronism).*

Clinical features Proximal RTA is seen in pediatric practice and the manifestations include growth retardation, malnutrition related to chronic acidosis, polyuria and nocturia related to hypokalemia. Distal RTA is seen in adults with similar features with the additional findings of nephrocalcinosis. Osteomalacic bone disease can occur with both proximal and distal RTA.

In Type IV RTA the features of the primary causative disorder dominate the clinical presentation.

Diagnosis An acid urine with a pH below 5.5 makes the diagnosis of distal RTA unlikely. Proximal RTA can be confirmed by demonstrating a fractional excretion of bicarbonate more than 15 per cent during a bicarbonate loading test. A urine pH above 5.5 necessitates an ammonium chloride loading test for diagnosing Type I (distal) RTA wherein the urine pH cannot be lowered (see earlier section).

Therapy Type I (distal) RTA can be treated with 1–2 mmol/kg/day bicarbonate to neutralise endogenous acid production. Alkali therapy itself corrects the hypokalemia and potassium supplements may not be necessary. Type II RTA (proximal) typically requires larger amounts of alkali (3–5 mmol/kg/day and potassium supplementation is usually required. Metabolic bone disease may respond to vitamin D. For Type IV RTA, therapy is directed towards correcting the serum potassium levels-fluorocortisone, 0.1 mg per day, when aldosterone is deficient and fluid overload absent, thiazide or loop diuretics when the patient is volume overloaded and hyporesponsive to aldosterone.

Both Type I and II RTA may be secondary disorders in which case the therapy is directed towards the primary disorder (multiple myeloma or heavy metal toxicity causing Type II RTA, or Sjogren syndrome, lupus erythematosus, hypercalciuria or amphotericin B administration causing Type I RTA).

Inherited Disorders of Tubular Function

These have been summarised in Table 14.6.

Acute interstitial nephritis

Acute interstitial nephritis seems to be a hypersensitivity reaction of the kidneys to exogenous agents, usually a drug.

Etiology Drugs implicated in the pathogenesis include non-steroidal antiinflammatory drugs (ibuprofen, indomethacin, tolmetin), diuretics (thiazides and furosemide), antibiotics (sulphonamides, methicillin, cephalothin, vancomycin) and other drugs (rifampicin).

Pathology and pathophysiology The glomeruli are normal but the interstitium is infiltrated by mononuclear cells and eosinophils. The mononuclear cells are T cells suggesting that a T cell-mediated delayed hypersensitivity reaction may be involved in the pathogenesis. The renal failure is due to an intraluminal block by sloughed-off cells and an increased intratubular pressure due to interstitial edema. It has also been speculated that failure to absorb the ultrafiltrate normally increases sodium delivery to the macula densa. This signals afferent arteriolar constriction, a mechanism referred to as tubuloglomerular feedback.

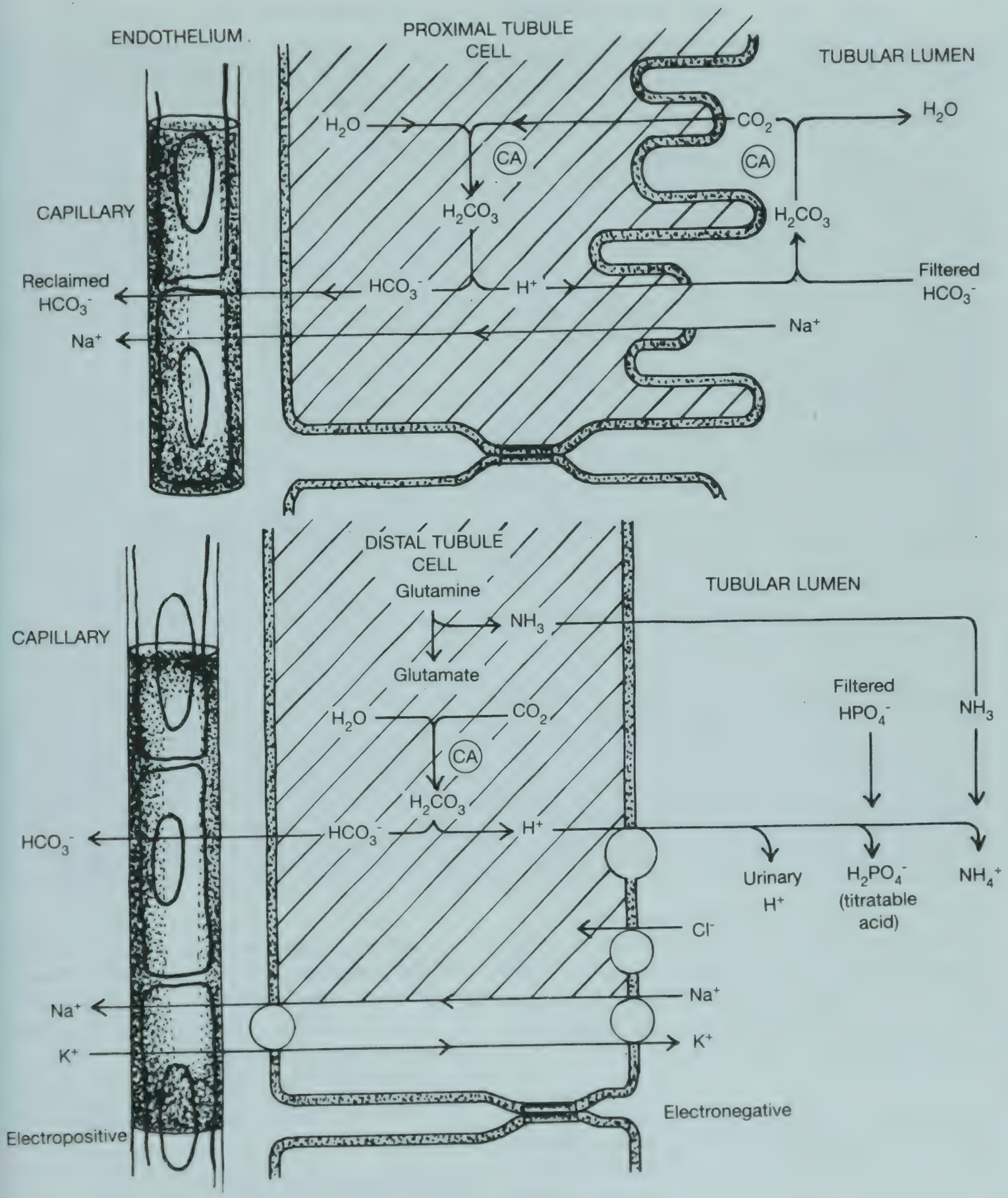


Fig 14.21 a and b: Renal tubular function. CA = carbonic anhydrase

Table 14.6 Some inherited disorders of tubular function

Disorder	*Defect*	*Inheritance*	*Clinical feature*
Renal glycosuria	inability to absorb glucose	AD	glycosuria
Hartnup disease	defective renal transport of tryptophan	AR	• pellagra-like rash • cerebellar ataxia
Fanconi syndrome	generalised proximal tubular dysfunction		• bone disease • polyuria • aminoaciduria
Cystinuria	defective renal transport of dibasic amino acids	AR	• cystine stones
Vitamin D-resistant rickets	inability to reabsorb phosphate	X-linked dominant	• rickets
Vitamin D-dependent rickets	defective 1-αhydroxylation of vitamin D_3 or defective receptor for 1,25 vitamin D_3	AR	• rickets
Pseudohypo-parathyroidism	renal tubules resistant to PTH	AD/X-linked dominant	• elevated serum phosphorus • hypocalcemia
Nephrogenic diabetes insipidus	renal tubules resistant to ADH	X-linked recessive	• polyuria • dehydration • hypernatremia
Bartter syndrome	diminished sodium chloride reabsorption by the loop of Henle	AR	• hypokalemia • metabolic alkalosis • polyuria • muscle weakness • tetany • no hypertension

Clinical features The disorder can vary in severity and commonly takes the form of an episode of acute renal failure associated with fever, eosinophilia and a rash. Oliguria may be seen due to a rapid decline in glomerular function.

Diagnosis The urinary sediment typically contains numerous leukocytes. Eosinophiluria (Hansel or Wright stain) is a prominent feature. Microscopic hematuria and varying degrees of proteinuria (usually <1 g/24 hours) are present.

Natural history and treatment The outcome of acute interstitial nephritis is variable. With drug induced disease, stoppage of the offending agent is accompanied by marked improvement of renal function. Occasionally, a chronic interstitial nephritis results. A short (one to two week) course of high dose steriods can accelerate recovery, especially in the oliguric patient.

Chronic interstitial nephritis

This is a chronic inflammatory process of the renal interstitium associated with interstitial fibrosis and loss of renal tubules.

Etipathogenesis The commonest cause is underlying urinary tract obstruction. Other causes include nephrotoxins (cadmium, lead, copper, mercury,) drugs (analgesics, gold, lithium), immune disorders (systemic lupus, Sjogren syndrome) and neoplastic disorders (myeloma, lymphoma).

Clinical features In general, in these disorders there is a relative preservation of glomerular function until late in the disease and a prominent impairment of tubular function earlier in the course. Thus, defects in the concentration and dilution of urine, acidification of urine and potassium excretion occur early. This results in polyuria, nocturia, metabolic acidosis and hyperkalemia in varying combinations.

Treatment and prognosis The prognosis depends on the specific cause as does the treatment. Urinary obstruction must be treated and exposure to the offending agent (drug or toxin) stopped immediately.

KEY CONCEPTS

Polycystic kidney disease

- PKD is an autosomal dominant disease with complete penetrance; the culprit gene is located on chromosome 16.
- Renal cysts consist of dilated tubules and glomeruli. They may be associated with hepatic cysts (30%) and cerebral aneurysms (10%).
- Clinical features of PKD include flank pain (60%), hematuria (30%) and systemic hypertension (60%). The kidneys are usually palpable in adults. An US or a CT scan is usually diagnostic. The diagnostic hallmark on an IVP is the *spidery* appearance of *calyces*.
- Treatment consists of controlling high blood pressure, and treating any intercurrent urinary or cyst infections. Almost 90 per cent of PKD patients progress to chronic renal failure. Old age, male sex and the presence of systemic hypertension worsen prognosis.

Type I (distal) RTA

- In this condition a defect in distal tubular secretion of H^+ ions results in hyperchloremic hypokalemic acidosis. It may be primary (autosomal dominant) or secondary (e.g., Sjogren syndrome, lithium intake, obstructive uropathy).
- The clinical symptoms are related to hypokalemia. Hypocitraturia with hypercalciuria results in nephrolithiasis and bone disease.
- An ammonium chloride load test is diagnostic; the urine pH remains >5.5.
- Treatment consists of bicarbonate replacement (small amounts); potassium supplements are usually not needed.

Type II (proximal) RTA

- The primary defect is in the renal tubular absorption of bicarbonate. This results in hyperchloremic acidosis with hypokalemia. It may be primary or secondary (e.g., Fanconi syndrome, Wilson's disease, multiple myeloma).
- Clinical manifestations include hypokalemia, hypovolemia and growth retardation (the latter in the inherited form of the disease).
- In the ammonium chloride load test, the urine pH falls below 5.5.
- Treatment consists of large doses of bicarbonate along with potassium supplements; the combination of a thiazide diuretic and a low salt diet is an alternative.

Type IV RTA

- This is the most common of the RTAs. The primary defect is in the secretion of potassium by the distal tubules. The condition may be due to reduced renin/aldosterone secretion (e.g., diabetes mellitus), or may result from tubular hyporesponsiveness to aldosterone (e.g., SLE, sickle cell disease, obstructive uropathy).
- Presentation is a hyperchloremic hyperkalemic acidosis with mild renal failure. This condition is most often asymptomatic.
- No specific treatment is needed. Dehydration must be avoided. Occasionally, mineralocorticoid replacement may be required.

Acute interstitial nephritis

- AIN is a sudden reduction in renal function characterised clinically by a mild proteinuria, variable

hematuria, oliguria and pyuria. Such interstitial inflammation may be *idiopathic* or secondary to *drug toxicity* (analgesics, aminoglycosides, contrast agents), *infections* or *hypersensitivity reactions*. (Drugs like NSAIDs, d-penicillamine can cause AIN and there is prominent fever, rash and eosinophilia).

➢ In AIN, there is histologic evidence of interstitial edema, a PMN interstitial infiltrate and patchy necrosis of the tubules. Eosinophiluria is uncommon but pathognomonic of hypersensitivity nephritis.

➢ Treatment of AIN is similar to ARF; any suspected offending drug must be stopped immediately; a trial of high dose steroids is warranted.

Chronic interstitial nephritis

➢ Causes of CIN include obstructive uropathy, metabolic diseases (diabetes mellitus), systemic diseases (Sjogren syndrome), drugs, (analgesics, heavy metals), and sickle cell disease.

➢ There is histologic evidence of tubular dilatation with tubular casts; this is accompanied by a mononuclear interstitial infiltrate and areas of interstitial fibrosis.

➢ The symptoms of CIN are related to defective urinary acidification and concentration by the renal tubules; these include polyuria and nocturia. Proximal tubular disorders present with a Fanconi type of syndrome (aminoaciduria, glycosuria) while manifestations related to aldosterone resistance predominate in distal tubular disorder. In CIN the following features are uncommon: peripheral edema, heavy proteinuria/ hematuria and hypertension.

➢ Treat any reversible causes.

14.7 Urinary tract infections

Urinary tract infection refers to the microbial invasion or colonisation of any part of the urinary tract. Several terms used in this context are to be understood. *Urethritis* and *prostatitis* refer to infections of the urethra and prostate gland. *Cystitis* refers to infection of the bladder. *Acute pyelonephritis* is the infection of the kidneys, *chronic pyelonephritis* is essentially a radiologic entity with findings of cortical scarring and pelvicalyceal deformity. *Significant bacteriuria* is finding more than 10^5 organisms per ml of urine and may or may not be symptomatic; when it is not symptomatic, the term *asymptomatic bacteriuria* is used.

Epidemiology Community acquired infections of the urinary tract occur mainly in women. The incidence of bacteriuria in girls is 1–2 per cent and increases with age at an approximate rate of one per decade of life. Pregnant women have an incidence of bacteriuria of 5–10 per cent as do elderly women. Symptomatic infections are largely confined to sexually active young women, men over the age of fifty and catheterised patients; it is called 'nosocomial' or *'catheter-associated' infection* in the latter category.

Etiopathogenesis The hyperosmolar environment of the medulla, the acid pH of urine, the flushing role of micturition, vesical mucosal antibodies, mucosal leucocytes and antibacterial properties of prostatic secretions constitute the normal body defence against urinary microbes (Fig 14.22). However, certain organisms especially the *Escherichia coli* strains, with large amounts of K (capsular) antigen and a special pilus (p-pilus)[1] for adhering to the uro-epithelium, can breach this defence and invade the urinary tract. Klebsiella and Proteus species can also invade (in the presence of obstruction of the urinary tract) and cause most of the hospital-acquired catheter-associated infections, along with the Pseudomonas species. The Candida species can colonise and invade the urinary tract in diabetics. *Mycobacterium tuberculosis* and *Neisseria gonorrhoea* are other agents which can infect the urinary tract. In prepubertal girls, coagulase negative *Staphylococus saprophyticus* is a common uropathogen. Most community-acquired infections are due to ascending infection of perineal coliform microbes. Hematogenous spread of infections can occur during any bacteremia. The short urethra, proximity to the perineum and the likelihood of trauma to the urethra during coitus account for female susceptibility to and predominance in urinary tract infections. Other predisposing causes include urinary stasis (neurogenic bladder, obstruction as in urinary calculus disease), anatomical abnormalities (vesicoureteric reflux), impaired resistance (diabetes mellitus) and altered vaginal flora (diaphragm or oral contraceptive induced) (Fig 14.22).

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[1] Pilus or fimbria is the bacterial organella for mucosal attachment.

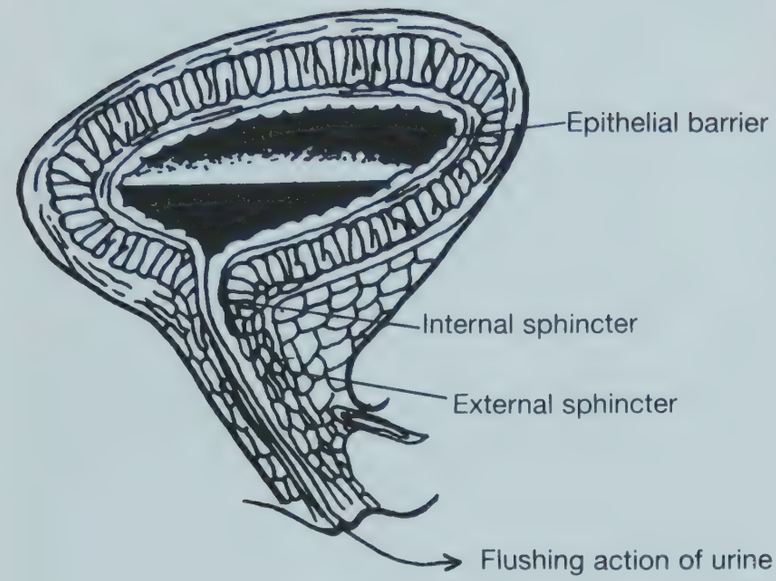


Fig 14.22 Normal defence mechanisms against UTI. In women the shorter urethra allows easier access to the bladder.

Clinical presentation Infections of the lower urinary tract (cystitis, urethritis, prostatitis) present with voiding problems such as frequency, urgency, dysuria and suprapubic pain. Infections of the upper urinary tract manifest with systemic features such as fever with chills and local flank pain (Fig 14.23). It is to be emphasised that *clinical distinction between the two may be extremely difficult as dysuria and frequency are not uncommon in upper urinary tract infections and fever with flank pain may occur in lower urinary tract infection*. Moreover, infection at the two sites may coexist, the lower urinary tract infection ascending to involve the kidneys. However, shaking chills, very high grade fever (>40°C) and septicemia favour the diagnosis of upper urinary tract infection. Catheter-associated infections are usually mild with minimal symptoms and low grade fever, although on occasion they too can be severe.

Diagnosis A rapid diagnosis of urinary tract infection can be made by the demonstration of any bacteria on a Gram stain of a centrifuged sample of urine. This roughly correlates with quantitative culture estimates of $>10^5$ bacteria per ml of urine. Urine collected as a 'clean catch midstream sample' must be refrigerated immediately if a delay of more than two hours in culture-plating is likely. Urine culture results yield antibiotic sensitivities and establish whether bacteriuria is significant (that is, more than 10^5 bacteria per ml). Colony counts of 10^2–10^4 organisms per ml may be significant if:

1. the urine is a suprapubic aspirate or a catheter specimen,
2. the patient has significant frequency and dysuria and has received antibiotics, and
3. in the presence of renal calculus disease.

Urinalysis may also reveal leucocyte casts (which strongly suggests upper urinary tract infection) or pyuria (defined as more than 10 WBCs/high power field). Leucocytosis in the blood favours a diagnosis of upper urinary tract infection.

Complications The three dreaded complications of upper urinary tract infection are renal papillary necrosis, renal abscess formation and its perirenal extension as a perinephric abscess.

Treatment Certain broad principles are well-recognised regarding the decision to treat urinary tract infections, the choice of the antibiotic and the dosage regimen used.

Symptomatic urinary tract infection requires treatment unless the urine cultures are negative and there is no pyuria in which case the patient probably has a *'frequency–dysuria' syndrome*. Community-acquired infections can be treated without waiting for urine culture results as the organisms are usually sensitive to several antibiotics. Hospital-acquired infections are treated with appropriate guidance of culture-determined antibiotic sensitivities. If cultures are negative and pyuria is persistent, a search is made for organisms like *Mycobacterium tuberculosis* or the Neisseria species. A diagnosis

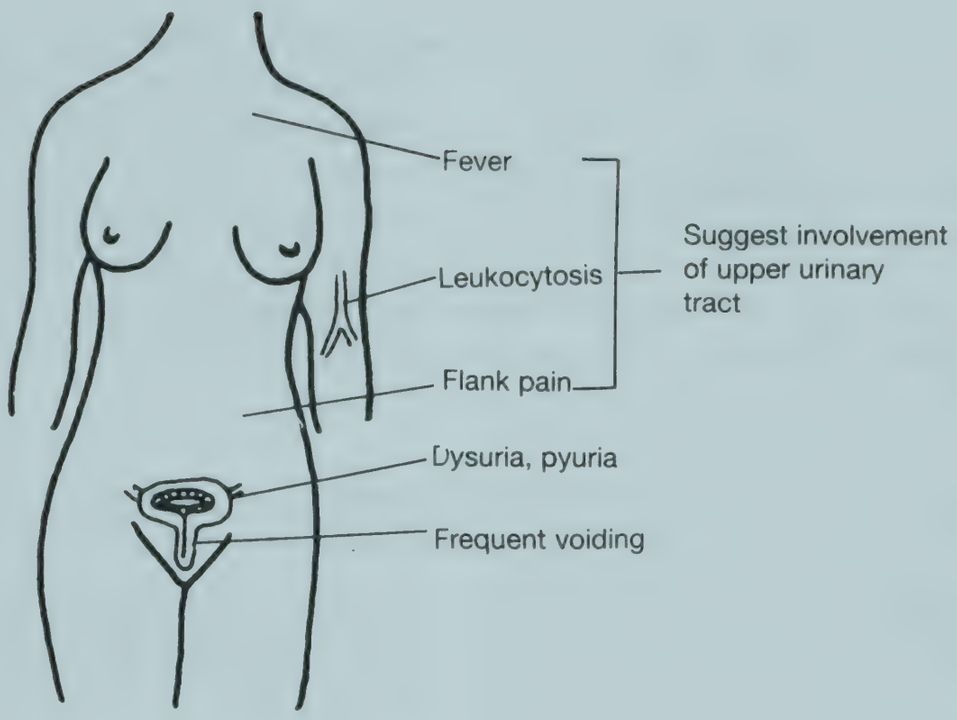


Fig 14.23 Clinical features of urinary tract infections

of vaginitis or non-gonococcal urethritis (with infection by Chlamydia) must also be excluded. Uncomplicated lower urinary tract infection in non-pregnant women without urologic abnormalities can be treated with either a single dose regimen (3 g amoxicillin, six single strength tablets of trimethoprim-sulfamethoxazole combination, 1 g sulfonamide) or a three-day course given empirically. This regimen is inexpensive, ensures compliance and is likely to be free of side effects. Men and pregnant women require a 7–10 day course of antibiotics. Urine cultures are by and large not required in lower urinary tract infections.

Upper urinary tract infection requires a two-week course of an appropriate antibiotic (nitrofurantion, trimethoprim-sulfamethoxazole, an aminoglycoside, cephalosporin or ampicillin-amoxycillin). Asymptomatic bacteriuria should be treated in pregnancy (wherein there is a one-in-five chance of acute pyelonephritis), in the diabetic or in those with underlying disease (neurogenic bladder). Catheter-associated mild infection usually responds only to the removal of the catheter.

The patients are also advised to consume adequate water (at least two litres a day), and a urinary analgesic such as phenazopyridine (pyridium) is prescribed if there is marked dysuria. There is little evidence to recommend the use of urinary antiseptic agents.

The patients are followed up with repeat urine cultures at 10–14 days after therapy. *Relapse* is defined as infection by the same strain within two weeks and should prompt a search for any suppurative focus or urologic abnormalities and a recheck of antibiotic sensitivities. *Reinfection* is defined as repeated infection by the same or different strain two weeks after the initial event and should also prompt a search for underlying urologic abnormalities such as calculus disease or vesicoureteric reflux. Even a single episode of upper urinary tract infection in a young male requires further urologic investigation along the above lines. Persistent pyuria with negative urine cultures *(sterile pyuria)* despite adequate antibiotic therapy requires the consideration of alternative diagnoses: analgesic nephropathy, urinary tuberculosis, calculus disease, chemical cystitis (for example, following cyclophosphamide

therapy) or a collagen vascular disease such as systemic lupus erythematosus.

Prognosis In the absence of underlying disease, the prognosis is excellent for both upper and lower urinary tract infection.

Prevention and prophylaxis Women with more than two episodes of urinary infection over a six-month period may benefit from a three-month course of daily prophylactic single dose trimethoprim-sulfamethoxazole (one tablet single strength) or nitrofurantion (50 mg). Preventive measures include proper asepsis during catheterisation, screening of all pregnant women for bacteriuria and its treatment when diagnosed.

KEY CONCEPTS

- UTI is more common in women and in elderly men. Usually UTI is due to perineal coliforms (most often E. coli is responsible).
- *Upper* UTI refers to infection of the kidneys or the renal pelvis. *Lower* UTI are due to infection of the bladder (*cystitis*), urethra (*urethritis*) or the prostate gland (in men; *prostatitis*).
- Classical symptoms of UTI include urinary urgency, frequency and pain. These symptoms are common to both lower and upper UTIs and do not discriminate between them. *Presence of flank pain, high fever and leucocytosis favour a diagnosis of upper UTI.*
- UTIs are diagnosed if there are $>10^5$ *organisms/ml* of urine on culture of a *clean catch mid-stream* urine specimen; a lower colony count on urine culture may also indicate UTI if the specimen is obtained from an indwelling catheter or if the patient has been partially treated with antibiotics. There may be associated pyuria. A colony count of $>10^5$ organisms /ml may exist without symptoms (*asymptomatic bacteriuria*) in pregnant women, in diabetics and in those with underlying pathology of the urinary tract (such as neurogenic bladder).
- Lower UTIs are treated with cotrimoxazole, fluorinated quinolones or amoxicillin (with clavulanate) for upto 3 days. Upper UTIs are treated with antibiotics for longer periods (two or more weeks). Asymptomatic bacteriuria should be treated in the pregnant patient.

14.8 Renal calculus disease

Nephrolithiasis is the deposition of calcaneous material in the renal papilla, pelvis and calyces and must be differentiated from *nephrocalcinosis* in which calcification occurs within the renal parenchyma. The two disorders may or may not coexist.

Epidemiology Northern India is part of a *stone belt* (Fig 14.24) that stretches from Iran to Indochina. Renal calculi account for five per 1,000 hospital admissions in north India. The only climate factor responsible for this predilection is possibly chronic dehydration. This, however, does not explain why the entity is less common in the hot and dry parts of south India. There is also an unexplained male predominance (M:F = 3:1), except the hyperparathyroidism-related stones and struvite stones which occur more often in women. The disorder usually presents in the third decade of life or later.

Etiopathogenesis The process of calculus formation involves the excretion of a solute in such large quantities that the *equilibrium solubility product* (defined as the quantity of solute which remains stable in solution) is exceeded. The nucleus of the calculus is a precipitating crystal and organic colloids constitute the *matrix*. When the nucleus differs from the subsequent crystals which settle (such as, calcium oxalate on a uric acid crystal), the phenomenon is referred to as *heterogeneous enucleation*. The crystals grow by a process of layering one on top of another *(epitaxy)*. Most calculi require the presence of a triad of factors, that is, a solute which is in excess (hyperexcretion) or in an insoluble form, a solvent which is less in amount (dehydration) or altered in composition (abnormal pH), and the absence of endogenous inhibitors of calculus formation (citrates, pyrophosphates, magnesium and glycoproteins).

Calcium stones account for more than 80 per cent of renal calculi (70 per cent calcium oxalate, 10 per cent calcium phosphate stones) while magnesium ammonium phosphate (struvite) (10 per cent), uric acid (5 per cent) and cystine (<1 per cent) calculi account for the rest (Fig 14.25). A minority of stones (<3 per cent) are related to renal tubular acidosis, hyperoxaluria and xanthinuria. The vast majority of stone-formers in Europe and America have *hypercalciuria* (defined as >300 mg per 24 hours). The exact incidence of this disorder in Indian patients is not clear. The increased content of calcium in the urine may be related to increased dietary absorption *(absorptive hypercalciuria)* when it tends to be familial, or to renal calcium leak *(renal hypercalciuria)*. In the former (which accounts for over two-thirds of the cases), the serum calcium and phosphate levels tend to be in the normal range and the parathyroid hormone (PTH) is suppressed. In the latter, the primary abnormality is a renal tubular leak of calcium which is compensated by increased parathyroid hormone, with the result that normocalcemia and hypophosphatemia

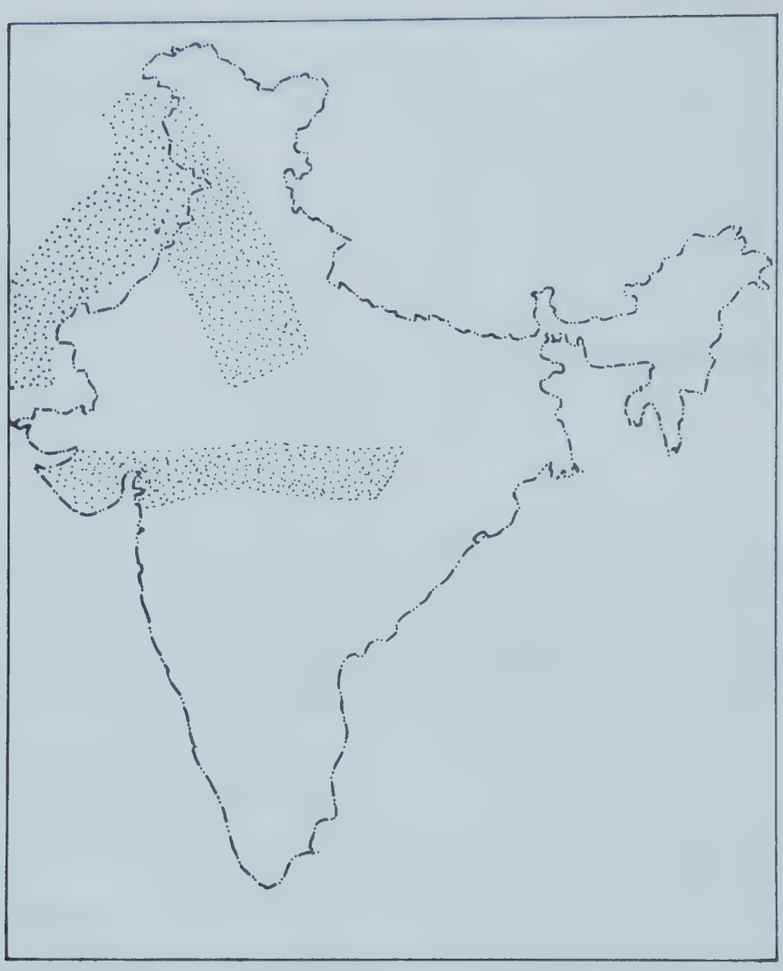


Fig 14.24 Belts of urinary calculus in India and Pakistan

ensue. A third rare cause of hypercalciuria is hypercalcemia due to any cause such as primary hyperparathyroidism, prolonged immobilisation, multiple myeloma and Cushing syndrome. These disorders may also be associated with calcium stones. Calcium phosphate stones tend to form in alkaline urine whereas calcium oxalate stones are urine pH independent. Hyperoxaluria is a rare disorder associated with either ileal disease (ileal surgery or inflammation) or occurring as a rare genetic disorder. In ileal disorders, the associated fat malabsorption increases intestinal luminal fats which bind calcium so that the oxalate (which is normally excreted by complexing with calcium) is available for abnormal excessive absorption.

Uric acid stones are found in hyperuricosuric conditions (defined as >600 mg per 24 hours urine) such as primary gout or myeloproliferative syndromes. Hyperuricosuria is often seen in calcium oxalate stone-formers where the uric acid crystals act as 'heterogeneous' enucleators. Most patients with uric acid stones do not have clinical gout. Uric acid stones form in acidic urine.

Struvite or triple phosphate stones are found in women with urinary infection due to urease forming organisms such as the Proteus and Klebsiella species. Bacterial urease degrades urea into ammonia and the latter is trapped with hydrogen ions and triphosphates as magnesium ammonium phosphate. These stones tend to assume a stag-horn configuration in the renal pelvis and form in alkaline urine. Cystine stones form in acid urine in disorders associated with renal leak of cystine, usually with other diabasic amino acids (COAL – Cystine, Ornithine, Arginine and Lysine).

In distal renal tubular acidosis, the combination of hypocitraturia, alkaline urine and hypercalciuria (the last being due to acidosis-promoted renal calcium leak) leads to calcium phosphate stones.

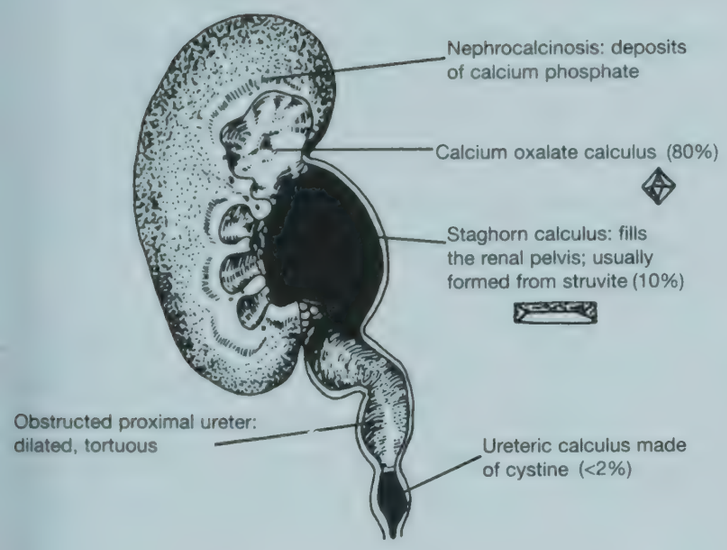


Fig 14.25 Types of renal calculus disease

Clinical features The calculus in the renal papilla may be silent and be discovered incidentally in an abdominal roentgenogram in an *asymptomatic* patient. It may slip into the renal pelvis and ureter and cause pain, obstruction, bleeding and infection.

1. When the stone occludes the pelvis, there is a consequent dilatation of the kidney and the urinary collecting system which is painful and is known as renal colic. The pain occurs in the costovertebral angles and reaches a peak intensity in 30 minutes.
2. A stone in the lower third of the ureter causes the characteristic pain in the flank which radiates along the lateral and anterior abdomen to the groin, a pain called *ureteric colic.* Calculi in the ureterovesical junction frequently present without colic but with dysuria, frequency and urgency, which are manifestations of inflammation of the trigone (trigonitis).
3. The irritation of the mucosa by the stone can lead to ulceration and bleeding– hematuria– and may be gross or microscopic.
4. When portions of the stone disintegrate and are passed in urine, *graveluria* results.
5. When the obstruction is chronic and at the pelvis, the kidney dilates along with the calyces and the pelvis and is referred to as *hydronephrosis, hydrocalcycosis* and *hydropelvis,* respectively.
6. When there is ureteric obstruction, the proximal ureter dilates and this is called *hydroureter.* The obstruction predisposes to a chronic interstitial nephritis.
7. Urinary obstruction also prediposes to acute ascending infection of the kidneys known as *acute pyelonephritis.*
8. The process may become chronic with cortical scarring and is known as *chronic pyelonephritis.*
9. Sometimes the infection is fulminant and is caused by pyogenic organisms, the kidney then becomes a bag of 'pus' – this is known as *calculus pyonephrosis.*
10. Sometimes stag-horn calculi (Fig 14.26) get chronically infected with species like Proteus and the resulting pathology is strikingly different–it is called *xanthogranulomatous pyelonephritis.* These are areas of tissue necrosis surrounded by xanthomatous cholesterol laden foamy histiocytes.
11. On occasion, the calculi can obstruct both ureters and *calculus anuria* results.
12. Chronic obstructive uropathy may also eventually lead to *chronic renal insufficiency.*

Diagnostic approach All patients with renal calculus disease should have an X-ray film of the abdomen, urinalysis, urine culture and a blood screening test. Serum biochemistry may reveal hypercalcemia suggesting hyperparathyroidism, hyperuricemia suggesting gout, or a hyperchloremic metabolic acidosis suggesting renal tubular defect in acidification. Serum creatinine and blood urea levels reflect the functional effects of the calculi on the kidneys. At least two 24-hour collections of urine are subjected to measurement of urinary calcium (normal values 50–150 mg/24 hours), oxalate (normal values

Fig 14.26 Plain X-ray of abdomen (KUB) of a 50-year old woman with recurrent renal colic. Note the stag-horn calculus in the left kidney.

5–45 mg/24 hours), cystine (normal values upto 70 mg/24 hours) and uric acid (normal values 30–100 mg/24 hours). Microscopic and crystallographic analysis of any stone passed is inforrmative. Xanthine and uric acid stones are radiolucent. The sulphur content of cystine stones render them radio-opaque. Calcium stones and struvite stones are densely radio-opaque. Radiolucent renal calculi are detected by ultrasonography. Secondary effects such as hydronephrosis can also be seen with ultra-sonography. When tubular dysfunction (RTA) is suspected, the pH of an early morning sample of urine is measured. If it is more than 6 pH units, a short ammonium chloride loading test may be performed for establishing the diagnosis of distal renal tubular acidosis (see 'diagnostic methods').

When urinary hypercalciuria is detected, measurements of serum calcium, serum immunoreactive parathormone and fasting urinary calcium levels are used to differentiate the entities of primary hyperparathyroidism, renal and absorptive hypercalciurias (Table 14.7).

Treatment Medical treatment of renal calculus disease is aimed at preventing new stone formation and arresting the growth of preexisting stones. General measures advised for every stone-former include a liberal fluid intake, avoidance of calcium-rich food items, such as milk and other dairy products, and avoiding oxalate-rich food such as spinach, tea and beetroot.

Idiopathic absorptive hypercalciuria is treated with dietary restriction of calcium. Failure to lower urinary calcium with diet alone may necessitate the use of phosphate binders which will complex with intestinal calcium and prevent its absorption. If the serum phosphate levels are normal, non-absorbable sodium cellulose

Table 14.7 Differential diagnosis of hypercalciuria

Entity	*Serum calcium*	*Parathormone*	*24-hour urine calcium*	*Fasting urine calcium*
Primary hyper-parathyroidism	↑	↑	↑	↑
Renal hyper-calciuria	normal	↑	↑	↑
Absorptive hypercalciuria	normal	normal	↑	normal

phosphate (2 grams four times a day) can be used. For hypophosphatemic absorptive hypercalciuria, absorbable orthophosphates can be used. Renal hypercalciuria responds to thiazides (50 mg hydrochlorthiazide twice daily) or the potassium-sparing diuretic amiloride. Cystine stones respond to therapy with sodium bicarbonate administered orally to alkalinise urine (pH>7.5). Those with severe cystine stone disease may be candidates for d-pencillamine therapy (2.0 grams daily in divided doses) or irrigation therapy (intrarenal irrigation with acetylcysteine or mercaptopropionyl glycine).

Uric acid stones are also treated by making the urine alkaline and with allopurinal to lower the serum uric acid levels to the normal range.

Struvite stones are usually, stag-horn-shaped and require surgical therapy. Infection should be controlled with appropriate antibiotics. A trial of urease inhibitor acetohydroxamic acid (250 mg three times a day) may be effective in controlling infection-related stone formation.

Hereditary hyperoxaluria responds to pyridoxine therapy whereas enteric hyperoxaluria responds to a low-fat, low-oxalate diet combined with oral calcium 1–4 g/day in divided doses or cholestyramine (1.0 g four times a day). The last two drugs bind oxalate in the gut and prevent its absorption.

Surgical removal is required whenever renal calculus disease is complicated by infection, obstruction, recurrent bleeding or severe pain. A new alternative to surgery is mechanical fragmentation of the calculus by a focused, electrically generated shock wave: *lithotripsy.* The technique can be *extracorporeal, percutaneous* (through a flank incision) or *endoscopic* (passage of an ultrasonic transducer into the ureter). This therapy is relatively new and requires further clinical experience before a comparison with established surgical techniques can be made.

KEY CONCEPTS

Renal calculus disease

- Renal calculus disease may be due to calcium oxalate (especially in men), magnesium ammonium phosphate (*struvites*; more in women and related to urinary infections; have a stag-horn appearance), uric acid, xanthine or matrix stones.
- Calculi are formed due to a combination of three mechanisms: *supersaturation* (overexcretion of calcium), *nucleation* (uric acid stones) and a *reduced concentration of inhibitors* of calculus formation (reduced urinary citrate in hypocitraturia).
- Symptoms of renal calculi include hematuria, colic, chills and fever, graveluria and obstruction. *Complications* of renal calculus disease include urinary infection, calculus anuria, renal failure, hydronephrosis and pyonephrosis.
- Investigations include estimating serum calcium, phosphate and uric acid levels, renal functions, measurement of 24-hour urinary excretion of calcium and uric acid. Renal calculi are usually radio-opaque due to their calcium content; pure uric acid, xanthine and matrix stones are radiolucent. Ultrasonography is useful for diagnosis and for assessing the degree of hydronephrosis (if any) and other potential complications.
- The pain of acute renal colic is relieved with narcotics and antispasmodics. Treatment of renal calculus disease includes increased fluid intake, a low purine diet, allopurinol and alkalinisation of urine for patients with uric acid stones, and acidification of urine in patients with struvite stones. Thiazide diuretics are used in patients with hypercalciuria. Urinary alkalinisation and d-pencillamine are recommended in patients with cystine stones. If renal calculus disease results in urinary tract obstruction, recurrent infections or renal functional impairment, definitive measures may become necessary. Therapeutic options include surgical removal, extracorporeal short wave lithotripsy (ESWL), and endoscopic extraction (only for small stones in the lower urinary tract).

14.9 Tumours of the urinary tract

Benign Tumours of the Kidney

Renal adenoma

This is the most common benign tumour, occurring in the renal cortex. Lesions greater than 3 cm exhibit unpredictable biological behaviour and are hence treated as malignant.

Hamartoma/angiomyolipoma

These are found predominantly in adults with tuberous sclerosis and have a propensity for causing retroperitoneal hemorrhage.

Malignant Tumours of the Kidney

Only the 'Grawitz tumour' or renal cell carcinoma will be discussed here, Wilm's tumour being essentially a tumour seen in the pediatric age group.

Renal cell carcinoma (Internist's tumour, hypernephroma[1])

Epidemiology Renal cell carcinoma predominantly affects middle aged individuals and men more often than women (M:F = 2:1). Smoking is a definite risk factor. Hereditary forms occur in the setting of *von Hippel Lindau disease* (a disease associated with neuroretinal hemangiomas), when they tend to be multiple and bilateral. There is an association with HLA antigens DR 8, and translocation defects between chromosomes 3 and 8/11 have also been found. Adult polycystic kidney disease predisposes to renal malignancy. A more recently recognised predisposing entity is the *acquired renal cystic disease* which occurs in patients with end stage renal disease on a chronic hemodialysis programme (usually of three or more years duration). About one in ten such patients with acquired cystic disease develop various renal neoplasms including renal cell carcinoma.

Pathology The renal cell carcinoma arises from the cells of the proximal convoluted tubules. Histopathology may reveal the classic 'clear' cells that are lipid-laden or less common variants with 'granular' cells or 'spindle' cells. Biologically the tumour tends to invade vessels. It may metastasise extensively through arterial route (spreading to lungs, bones, liver and brain) or grow into and obstruct the inferior vena cava and hepatic veins. It may, in a retrograde manner, reextend into the pampiniform plexus resulting in a left varicocele. The paraneoplastic effects of the tumour (discussed latter) are a hallmark of its biological behaviour. Solitary metastases may occasionally regress. The tumour may also secrete various hormones, such as renin, parathormone, corticosteroids and gonadotropins.

Clinical features Gross hematuria is the commonest presenting feature, occurring in about half the patients. A palpable mass or flank pain (emphasised in earlier years) are distinctly uncommon and suggest extensive local spread of the tumour. Systemic features like malaise and

[1] This term has to be discarded as it refers to origin of the tumour from 'adrenal rests'.

weight loss occur frequently. Clinical presentation as anemia (seen in 50 per cent) or as pyrexia of known origin (10 per cent) can really test the internists' diagnostic skills. Production of renin-like substances can cause hypertension. Venous involvement and obstruction can result in hepatosplenomegaly with ascites (hepatic vein involvement) or a left-sided varicocele (left renal vein invasion).

Reversible disturbances in liver function tests (elevated alkaline phosphatase) in the absence of hepatic metastases is well known. Hormone secretion by the tumour may occasionally result in polycythemia or hypercalcemia. Secondary deposits of the tumour tend to be clinically silent.

Diagnosis The investigation of a renal mass has been extensively discussed in an earlier chapter

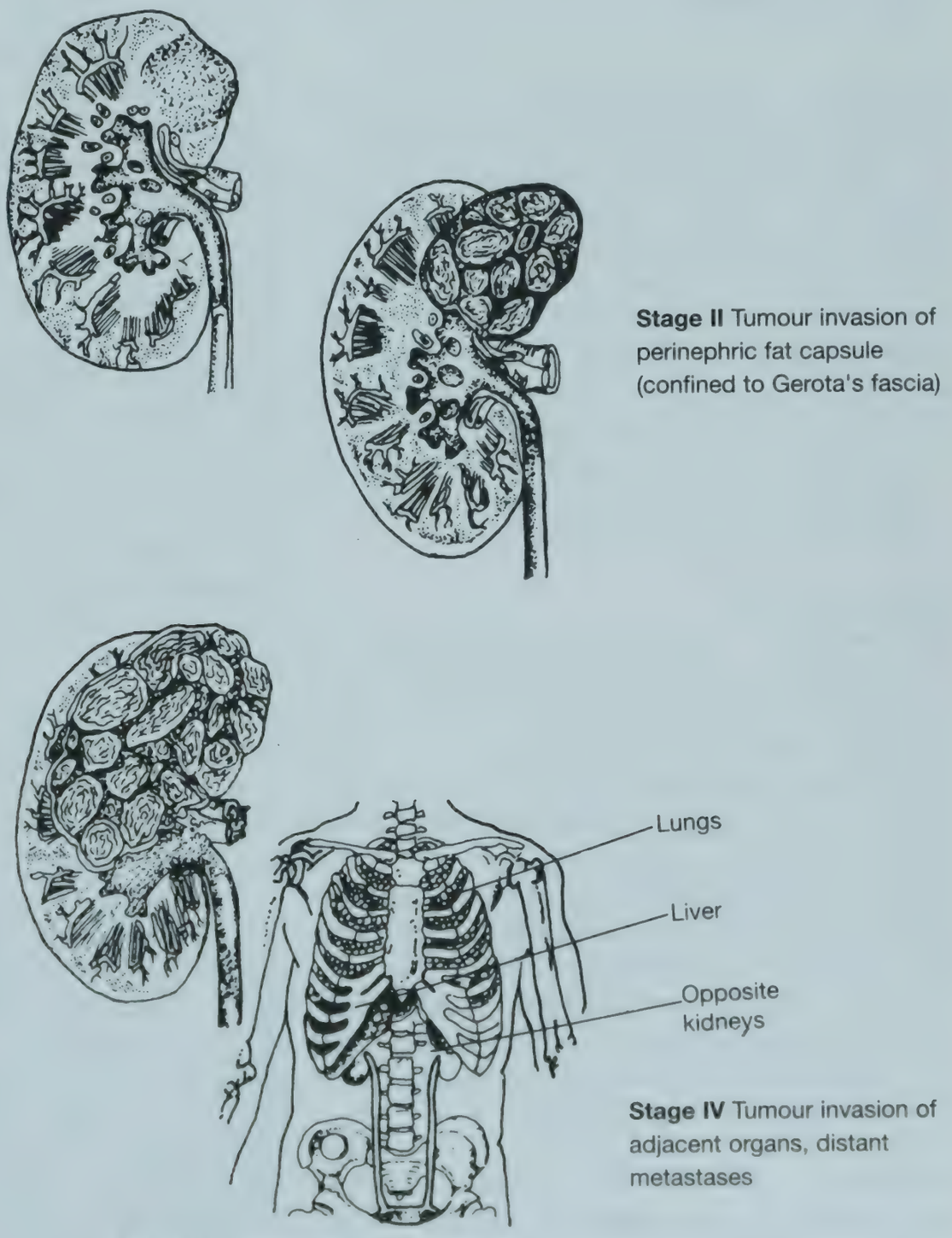


Fig 14.27 Potential sites of spread

(refer to earlier section on 'evaluation of the patient with hematuria'). To summarise briefly, a solid mass on ultrasound which shows contrast enhancement on a CT scan strongly suggests a renal cell carcinoma. Renal masses with indeterminate characteristics may necessitate renal arteriography, where neovascularity (tumour blush) suggests malignancy.

Once the diagnosis is suspected, a chest X-ray, bone scan and liver function tests can be ordered to evaluate potential sites of spread (Fig 14.27).

Treatment Broadly speaking, disease confined to the kidney (Stage I and II) may be treated by a radical nephrectomy. Variations of this approach include preoperative arterial embolisation to simplify surgery by rendering the operative field less bloody and a partial nephrectomy for highly localised small tumours. Local radiotherapy (pre- or postoperative) has no role and the trials of various modalities (chemotherapy, hormone therapy, immune enhancement) in metastatic disease (Stage III, IV) remain investigational with varying degrees of success being reported in literature.

Bladder cancer

Epidemiology Carcinoma of the bladder is more common than renal cell carcinoma. It is commoner in men and is likely to be seen after the fourth decade of life. There is an increased risk following industrial exposure to aromatic amines, and naphthylamines and hence this cancer is seen with greater frequency in workers in dye and rubber factories. Smoking, calculus disease and Schistosoma hematobium infection also predispose to bladder cancer as does the long term use of the antineoplastic alkylating agent, cyclophosphamide. Artificial sweeteners like saccharine and cyclamate have also been linked to bladder cancer in mice.

Pathology The majority of bladder tumours are transitional cell carcinomas. Squamous cell carcinoma arises in relation to vesical calculus disease and vesical schistosomiasis. Adenocarcinoma arises near the dome of the bladder perhaps in urachal remnants. Both squamous cell carcinoma and adenocarcinoma are biologically more malignant tumours and have a worse prognosis.

Clinical features The cardinal manifestations of bladder cancer are related to the tendency of the tumour to bleed and to irritate the bladder. Thus, gross hematuria is the commonest presenting feature. Symptoms of frequency, dysuria and urgency may also occur, though they are less common. Advanced malignancy may present with pelvic pain and symptoms of obstructive uropathy due to pelvic infiltration and infiltration of ureters.

Diagnosis Once non-glomerular hematuria is documented (see 'evaluation of patient with hematuria'), urinary cytology may establish the diagnosis of urothelial transitional cell carcinoma. Confirmation of the bladder as the site of tumour will, however, require cystoscopy. The cystosopic examination can be done under anesthesia; a biopsy of the tumour is taken and its pelvic extension assessed by bimanual examination. Pelvic CT scanning will also help in staging the tumour, based on its pelvic extension.

Treatment Bladder tumours can be classified for therapeutic purposes as 1) *superficial* (invasion limited to submucosa), 2) *invasive* (invading the vesical muscle and perivesical fat) and 3) *metastatic.*

Superficial cancers are treated with transurethral endoscopic resection. If the superficial tumours recur, they can be resected again and intravesical chemotherapy with thiotepa, mitomycin, doxorubicin or BCG instituted. Invasive tumours require radical cystectomy with pelvic lymphadenectomy. Metastatic disease requires systemic combination chemotherapy (cisplatinum, vinblastine and methotrexate with or without doxorubicin).

KEY CONCEPTS

Renal tumours

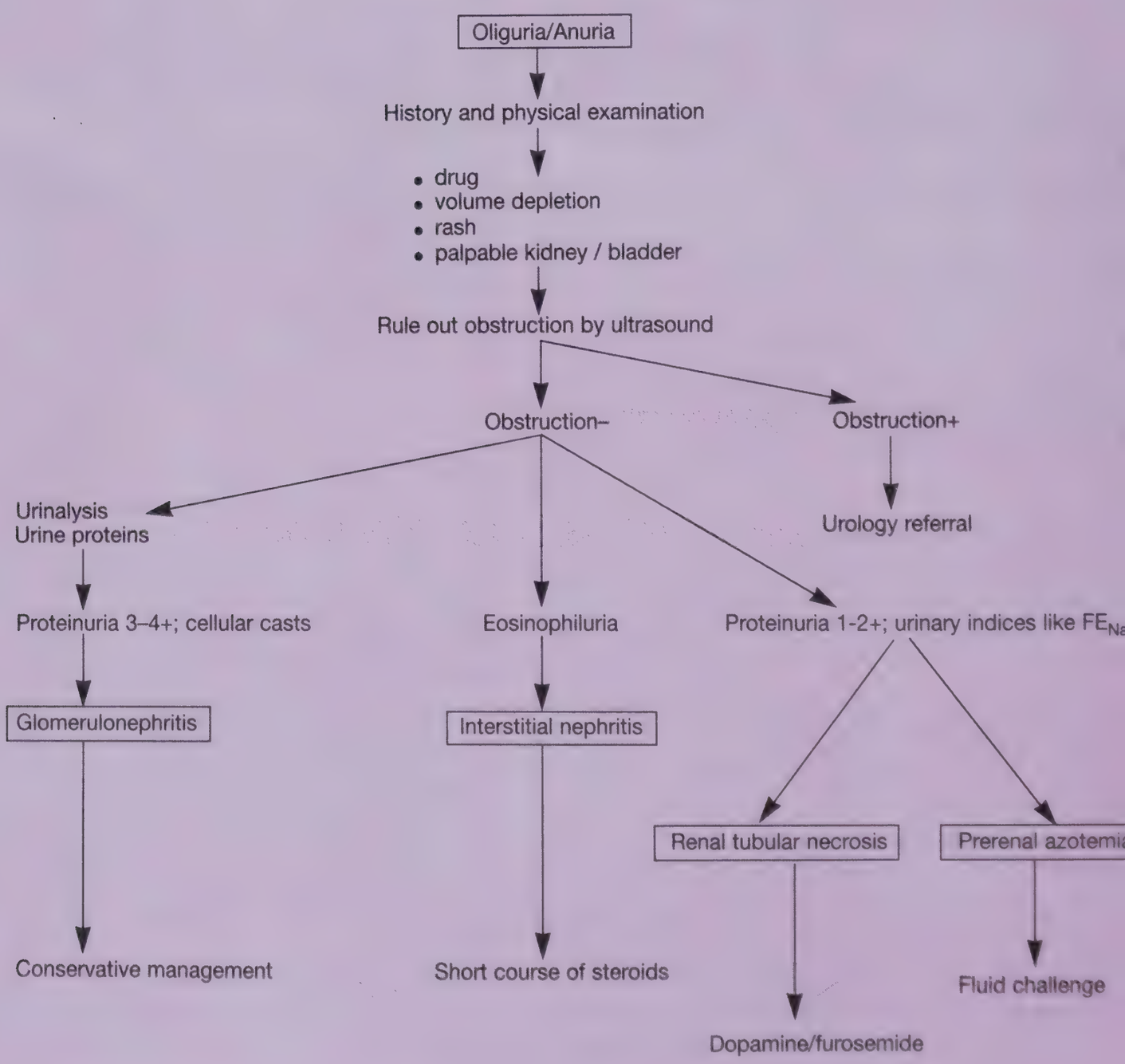
- *Adenocarcinomas* are the most common type of renal cancer. They occur in the fifth decade of life or later. The M:F ratio is 2:1. Renal cancers have been associated with smoking, and exposure to cadmium and thorotrast.
- Clinical presentation is usually with one or more components of the classic diagnostic *triad* of gross *hematuria* (70%), *flank pain* (50%) and a palpable abdominal *lump* (30%). The complete triad is present in <10%. Other unusual features include fever, hypertension, erythrocytosis, left-sided varicocele, and anemia.
- For diagnostic purposes, an US or an IVP is initially obtained and may be followed by a contrast CT scan. US-guided needle aspiration provides a tissue diagnosis. *Secondaries* typically involve the lungs, the liver, the bones and the adrenals. Metastases to these organs can be excluded with chest X-rays, a bone scan and LFT.
- For *Stages I–III* renal cancer, consider surgical resection. For *Stage IV* renal cancer, the outcome is poor; the tumour is relatively resistant to chemotherapy and to radiation.

Bladder cancer

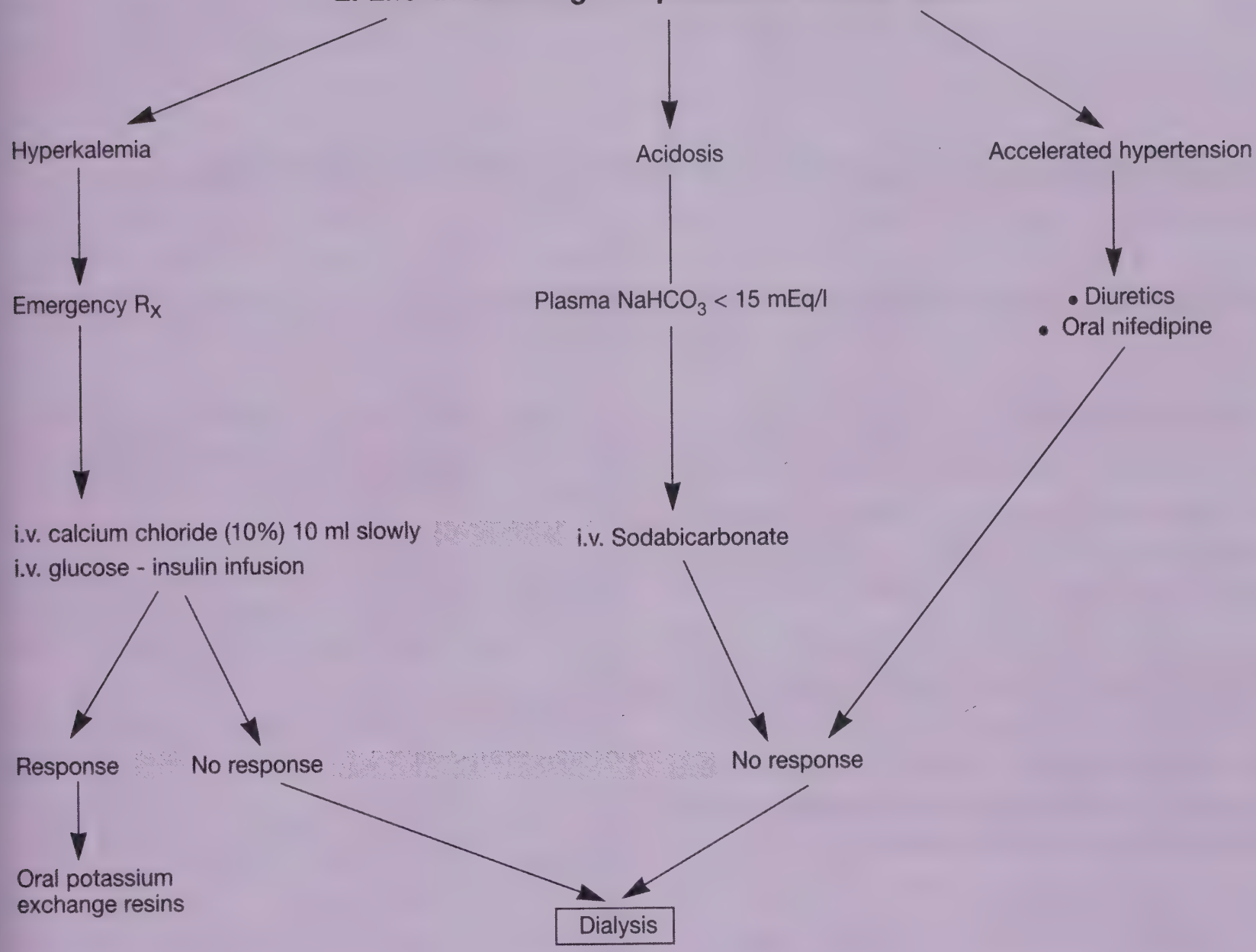
- 90% of bladder neoplasms are *transitional cell carcinomas*. The M:F ratio is 3:1. Bladder cancer has been associated with aromatic amines (aniline dyes, rubber and plastic industries), smoking and with cyclophosphamide use. *Squamous cell cancer* of the bladder is associated with Schistosoma hematobium infection and with bladder calculi. *Adenocarcinoma* of the bladder arises from urachal remnants on the bladder dome.
- Painless hematuria is a classic feature. Diagnosis is confirmed by urine cytology, and/or cystoscopy with biopsy. A CT scan, a chest X-ray and a bone scan are important investigations for staging bladder cancers.
- Superficial bladder cancer responds to *transurethral resection* with or without instillation of BCG or thiotepa. Bladder cancer which invades the wall but without any local or systemic metastases may be managed with *radical cystectomy*. Metastatic disease may be treated with *chemotherapy* (MVAC regimen).

14.10 Renal emergencies

1. Management of acute renal failure



2. Life-threatening complications in renal failure



15

Disorders of the Hematopoietic System

15.1 Basic physiology of hematopoiesis and hemostasis

Blood Components and Hematopoiesis

Blood is a liquid tissue best described as fluid plasma in which the formed elements erythrocytes, granulocytes, lymphocytes, monocytes, and platelets circulate within the intravascular space. Broadly, the principal functions of the various cellular elements are as follows : the red blood cell (RBC) carries oxygen to the tissues, the white blood cell (WBC) combat invasion by microorganisms, the lymphocytes provide immune-surveillance and the platelets promote hemostasis.

The red blood cells (RBCs)

The mature RBC is a biconcave disc containing hemoglobin, a complex protein comprising of iron-containing *'heme'* and a protein moiety, *'globin'*. A dynamic interaction between heme and globin gives hemoglobin its unique capacity to reversibly transport oxygen. Globin comprises of two pairs of polypeptide chains. To each of these chains one heme molecule is attached. In the normal adult there are three types of hemoglobin, depending on the polypeptide chains: HbA_1–$\alpha_2\,\beta_2$, HbA_2 – $\alpha_2\delta_2$ and HbF–$\alpha_2\gamma_2$.

Fetal and adult hemoglobin

In the fetus, the predominant hemoglobin is hemoglobin F. By the sixth month of gestation, HbF forms 90 per cent of the total hemoglobin and HbA constitutes the remaining 10 per cent. An orderly switch occurs during the course o gestation, wherein the gamma chains ar replaced by beta chains; as a result, at the time o birth, HbF level decreases to 70 per cent. By th age of six months, HbF decreases to less tha two per cent of the total hemoglobin. HbA_1 the becomes the predominant hemoglobin in th adult.

Hemoglobin A_1 can be detected as early a the sixteenth week of gestation, thus enablin antenatal diagnosis of abnormalities o hemoglobin synthesis. HbA_2, a minor adul hemoglobin, forms three to four per cent of th total hemoglobin content at the age o 12 months. In hemolytic anemias, the postnata reduction of HbF is retarded, resulting in greater proportion of HbF, a feature which help in the diagnosis of hemoglobinopathies.

Metabolism of the RBC Although the RB lacks both a nucleus and mitochondria, th mature RBC is metabolically active. Glucose utilised and lactic acid is produced by anerob glycolysis by way of the *Embden-Meyerh pathway.* Only 10 per cent of the glucose aerobically metabolised through the *hexos monophosphate shunt.* The energy generated b glucose metabolism is used for multip functions, a few of which are highlighted here: 1. maintenance of the integrity of the red c membrane cytoskeleton and its shape,

2. activation of the sodium-potassium ATPase pump, thus enabling potassium to remain within and sodium to remain outside the cell. If this cation pump fails, the red cells would swell and undergo spontaneous hemolysis, as is seen in congenital spherocytic anemia.
3. maintenance of the heme iron in the reduced state. Oxidative potentials within the cells can cause oxidation of the heme iron leading to its denaturation (*Heinz bodies).* Such cells are removed from the circulation by the splenic macrophages. Protection of heme iron from oxidation is provided by the H^+ released from NADH and NADPH which are byproducts of the energy pathways. Enzyme deficiencies in these pathways can thus result in hemolytic anemia such as glucose-6-phosphate dehydrogenase (G-6 PD) deficiency.
4. maintenance of adequate levels of adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (2,3-DPG) within the cell. ATP is a high-energy compound important for its contribution in cell metabolism. 2,3-DPG reduces the affinity of hemoglobin for oxygen thereby enabling oxygen release from oxyhemoglobin and its transfer to the tissues.

The life span of the RBC is 80 to 120 days. Ageing red cells are removed from the circulation by the mononuclear phagocyte cells within the spleen. The hemoglobin is broken down and the iron is retained for further heme synthesis.

The white blood cells (WBCs)

The mature granulocyte is the prime defender of the body against invading organisms. It achieves this purpose by its capacity to migrate into tissues in response to chemotactic stimuli, and by its capacity to recognise, phagocytose and digest the foreign material. Directional, active migration of the granulocyte is induced by chemotactic factors released by the bacteria, tissue necrosis, complement factors and by the white blood cells themselves.

Phagocytosis, an energy-dependent process, enables the membrane-bound hydrolytic enzymes within the cell to destroy the organism after engulfment.

The monocyte series

The monocyte is a large motile phagocytic cell 16–30 μm in size. It has a kidney-shaped nucleus containing a fine chromatin network with chromatin aggregates along the nuclear membrane. The cytoplasm stains blue-grey and is rich in *azurophilic*[1] *granules.* It originates from the totipotent stem cell within the bone marrow and later migrates into the blood, bone marrow, lymph nodes, spleen, liver, and other organ tissues. Its migration is in response to chemotactic stimuli. Within the tissue, the monocyte transforms into macrophages which have a very long life span.

The monocyte has numerous important functions which will be discussed in greater detail in the Immunology chapter. In brief, it is capable of phagocytosis, processing of antigens, induction of lymphocytes into a state of blast transformation, and elaboration of chemotactic and opsonising factors which promote phagocytosis. It also interacts with the lymphocytes to induce production of '*monocyte migration inhibition factor*'. Monocytes can undergo transformation into epitheloid cells in order to destroy intracellular pathogens such as mycobacteria.

The lymphocyte-plasma cell series

Morphologically, lymphocytes are classified into small, medium and large lymphocytes. On the basis of kinetic studies they can be divided into a long-lived and short-lived population. The long-lived cells form 70–80 per cent of the total lymphocytes; their life span extends to 100–200 days. The bone marrow derived cells, β-lymphocytes are responsible for antibody production. Thymic or T lymphocytes serve as effectors and regulators of the immune system.

The plasma cells range in size from 20–40 μm. The cytoplasm is basophilic and appears

[1] Azurophilic means with affinity for blue dyes.

mottled. The nucleus contains dense clumps of chromatin arranged to resemble the spokes of a wheel. It arises from the bone marrow stem cell and matures within 12 hours. Its life span after entry into the blood ranges from between two to four days. The plasma cell is seen in the peripheral blood only in diseased conditions and its chief function is synthesis of antibodies.

The platelet is an anucleate megakaryocytic fragment 3–5 μm in size. Its plasma membrane forms and opens into a canalicular system within the cell. The platelet is rich in granules which store chemicals that help in maintaining hemostasis.

Hematopoiesis

Hematopoiesis is an orderly process of cell proliferation and maturation which maintains the cellular elements necessary for the normal functioning of the body in the blood (Fig 15.1).

The earliest recognisable precursor, a *primitive blast cell,* divides to produce daughter cells, both of which are more mature than the parent cell. The daughter cells undergo further division and maturation. At each division the cells gain greater maturity, so that a stage is reached when terminal differentiation has occurred. At this state the cell has lost the ability to divide.

A small pool of *totipotent stem cells* capable of self-renewal and repopulating the bone marrow, exist throughout adult life. These cells give rise to the hematopoietic and lymphoid cell-lines. Hematopoietic growth factors are responsible for cell proliferation and differentiation. Differentiation means that the multipotent precursor is committed to a particular lineage, that is, erythroid or lymphoid cell-lines. The growth factors include:

1. *erythropoietin* which is responsible for erythropoiesis,
2. *colony stimulating factors* (CSF),
3. *interleukins* (IL-3 or multi-CSF).

Fetal hematopoiesis

Blood formation can be recognised in the human embryo as early as the third week of gestation. Large hematopoietic elements are scattered in the yolk sac. By the second month of gestation active hematopoiesis is established in the liver. Towards the beginning of the sixth month of gestation hematopoiesis shifts to the medullary spaces of the bones and at birth most of the blood formation occurs only in the red bone marrow. In the adult, active hematopoiesis is confined to the ends of long bones, sternum, ribs, vertebrae and the skull. *Extramedullary hematopoiesis* (for example, in the liver, spleen or lymph nodes), occurs only in diseased conditions after birth such as hemolytic anemia and myeloid metaplasia.

Erythropoiesis

In the marrow the red cell precursor, the *pronormoblast,* passes through various stages of maturity, during which time, the basophilic cytoplasm becomes hemoglobinised and the nucleus becomes condensed before being extruded out of the cell. The normal transit time between the pronormoblast and the red cell stage is seven days. When there is a demand for red cell production, the transit time within the bone marrow is shortened and the *reticulocyte* (immature RBCs) are prematurely released into the circulation.

Myelopoiesis

The earliest myeloid precursor cell is the *myeloblast.* It passes through various stages of development — promyelocyte, myelocyte (*mitotic pool*), the metamyelocyte and the band form (*non-mitotic pool*) — before transforming into the mature segmented neutrophil (Table 15.1). As the cells mature, they become smaller and their cytoplasm becomes less basophilic. The nucleus undergoes segmentation. Cytoplasmic granules with their characteristic staining properties appear. These differentiate the granulocytes into neutrophils, basophils and eosinophils.

Transit time within the marrow through the various stages of maturity is seven days, of which four to five days are spent in the non-mitotic

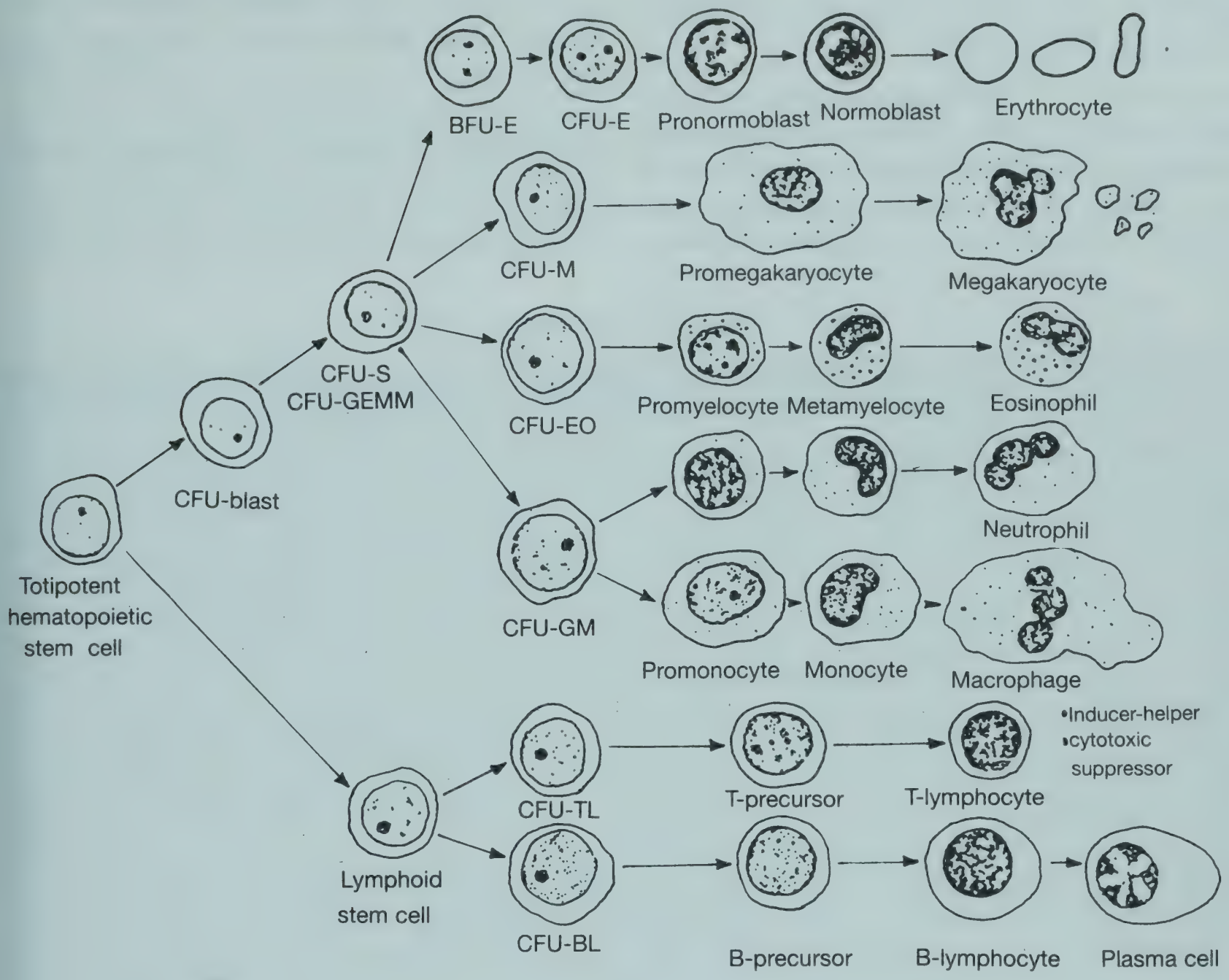


Fig 15.1 Cytogenealogy of blood cells

pool. The latter forms a reserve compartment from which the white blood cells are drawn to combat infection in times of need.

In the bloodstream, the neutrophils exist in two approximately equal pools. There is a *circulating pool* in the blood in which the neutrophil spends only 14 hours and a *marginated pool*, wherein the neutrophil marginates along the postcapillary venules. These marginated cells are not represented in the peripheral blood counts. The marginated neutrophils enter the tissues before undergoing cell death. Granulocytes located within the bone marrow, blood and along blood vessels can all be recruited to combat infection.

Megakaryocytopoiesis

The *megakaryocyte*, the platelet precusor, produces between 4000–8000 platelets per cell. Thirty per cent of the platelets are sequestered within the spleen and other extravascular sites after release. The life span of the platelet is nine days. Unlike neutrophils, there is no reserve pool of platelets within the bone marrow. During

situations of stress, as in acute blood loss, platelets are thrown into the circulation principally from the spleen.

Lymphopoiesis (Table 15.1)

The lymphoid system is derived from the same totipotent hematopoietic stem cell as the rest of the hematopoietic system. Commitment to the lymphoid lineage occurs early after which the lymphoid precursors migrate to other lymphoi organs like the thymus where furthe proliferation, differentiation and maturatio take place.

Physiology of hemostasis The blood maintai a finely-tuned balance between clotting ar fluidity. Injury to the vessel wall initiates a seri of interrelated reactions involving blood vessel

Table 15.1 Cells of the myeloid and lymphoid series

Cell	*Morphologic features*	*Physiologic function*	*Location*
Myeloblast (15–20 μm)	large nucleus, fine chromatin, usually two or more nucleoli; clear scant cytoplasm	proliferation	confined to bone marrow except in disease
Myelocyte	nuclear chromatin coarsens; nucleoli disappear; cytoplasm less basophilic, more abundant; prominent cytoplasmic granules develop	progressive differentiation	confined to bone marrow except in disease
Segmented cell (12–15 μm)	band-shaped to multilobed nucleus; coarse chromatin nuclear 'drumstick' (Barr body) in 3% normal female cells	motility, chemotaxis, immune adherence, phagocytosis, and lysosomal digestion	bone marrow, peripheral blood, tissues
	neutrophilic, eosinophilic or basophilic cytoplasmic granules	glycolysis provides energy for phagocytosis, protein synthesis continues	
Lymphoblast	large nucleus, fine chromatin, usually a single nucleus; clear cytoplasm	proliferation	germinal centres of lymph nodes, spleen, tonsils, gut and other sites not present in blood
Lymphocyte	small (4–10 μm); rounded, deeply staining nucleus; masses of chromatin, no nucleoli	transformation to immunoblasts, plasma cells; cell-mediated immune responses	lymphoid tissues, peripheral blood, bone marrow
	large (10–20 μm); cytoplasm clear, deeply basophilic to light	antibody synthesis	tissues
Plasma cell	large (20–30 μm), eccentric, oval nucleus; dense, coarse chromatin, basophilic cytoplasm, often vacuolated; perinuclear clear zone	antibody synthesis	lymph nodes, bone marrow tissues, not present in blood

platelets and clotting factors, resulting in the formation of a hemostatic plug.

Blood vessels

Reflex vasoconstriction occurs immediately after vessel wall disruption, thereby slowing the flow of blood at the site of injury. Serotonin and thromboxane are vasoactive products which are released by the platelets in order to enhance vasoconstriction.

Platelets

The endothelial cells lining the vessels prevent contact between blood and the underlying collagen. These cells not only form a physical barrier but also synthesise prostacycline, PGI_2, a potent vasodilator and inhibitor of platelet aggregation. Endothelial cells have two surface molecules — *thrombomodulin* and heparan sulphate. Thrombomodulin binds with thrombin to form a complex which can activate *protein C*, a powerful anticoagulant circulating in plasma. Activated protein C is responsible for proteolysis of coagulation factors V and VIII. Heparan sulphate binds with antithrombin III (also circulating in plasma) and inactivates thrombin and coagulation factors IXa and Xa (Fig 15.2).

In effect, the intact endothelial cell contributes significantly to the maintenance of fluidity of blood.

Injury to these cells results not only in their losing their anticoagulant properties, but also exposes the underlying *von Willebrand factor* (VWF) to the platelets, thus enhancing platelet adhesion at the site of injury.

As mentioned earlier, platelets are anuclear megakaryocytic fragments, rich in a variety of factors which enhance platelet aggregation. When the platelet comes in contact with the subendothelial collagen, changes occur within the internal milieu of the cell which leads to the release of thromboxane A_2. The latter is a potent vasoconstrictor and aggregator of platelets. Further, it induces platelets to release a wide variety of factors which are responsible for platelet aggregation, such as calcium, adenosine diphosphate (ADP), VWF and fibrinogen. Of these, ADP is of particular importance since it is responsible for inducing more and more platelets to undergo adhesion and aggregation, in order to form thrombin. The interaction of platelets with the endothelium and with other platelets is due to specific membrane receptors. The platelet membrane glycoprotein Ib binds to the VWF which in turn crosslinks with subendothelial collagen. This promotes adhesion of platelets to the endothelium. The platelet membrane glycoprotein IIb/IIIa is a receptor for fibrinogen. Thus platelet aggregation is

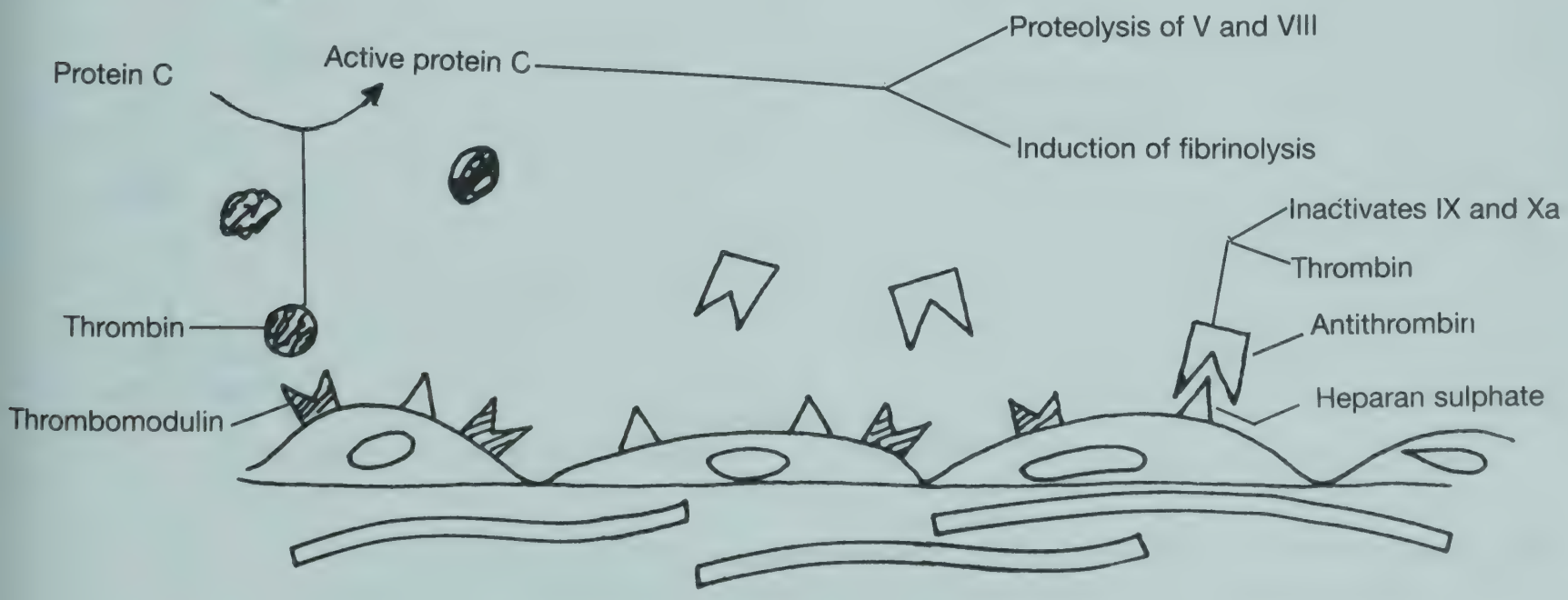
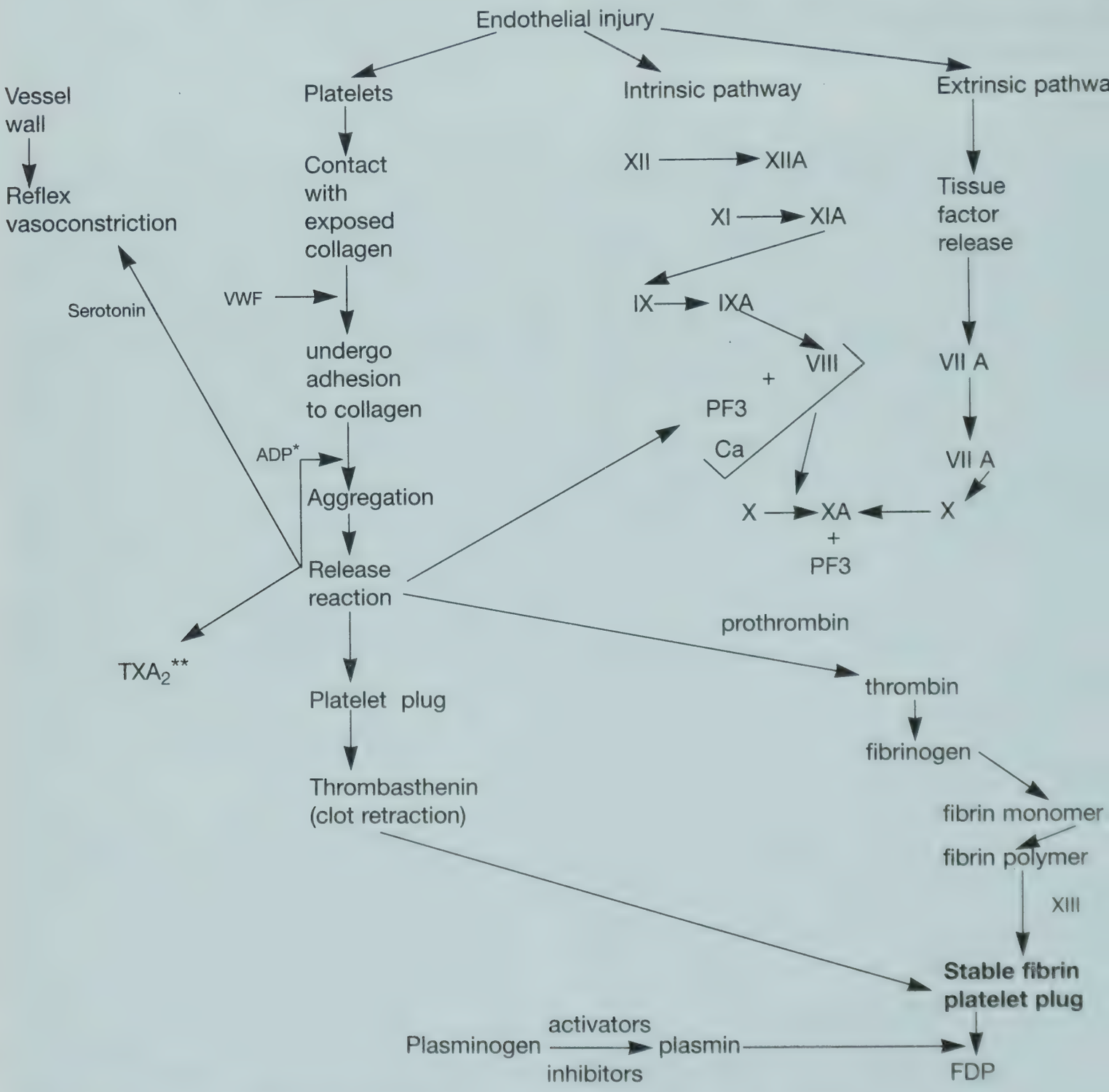


Fig 15.2 Inhibitors of activated coagulation factors

promoted by the binding of platelets to fibrinogen.

Coagulation cascade

Coagulation cascade is an enzymatic process by which soluble fibrinogen is converted to insoluble fibrin. In the *extrinsic pathway*, tissu thromboplastin is released when the vessel wa is injured. It activates factor VII which in tu activates factor X. The *intrinsic pathway* triggered when blood comes in contact with th collagen exposed after endothelial injury. Fact



*ADP exposes more receptors on platelet surface leading to platelet aggregation
** TX A_2 causes platelets to aggregate and contract to form a stable hemostatic plug

Fig 15.3 The coagulation cascade

XII is activated first. By a series of enzymatic steps factors XI and IX are also activated on the platelet surface. Activated factor IX and factor VIII interact with calcium to activate factor X. Activated factor X (*common pathway*) and activated factor V interact with calcium (still on the platelet surface) to catalyse the conversion of prothrombin to thrombin. Thrombin converts fibrinogen to fibrin monomers. Factor XIII in the activated form converts the monomers to fibrin polymers and forms a stable clot (Fig 15.3).

Coagulation is confined to the site of injury by simultaneous activation of the *fibrinolytic pathway*, inhibition of activated coagulation factors and rapid blood flow. Plasminogen, a factor present in plasma, is the most important component of the fibrinolytic pathway. It is activated to form plasmin, a protease which digests the fibrin clots.

15.2 Approach to a patient with hematologic disease

Approach to a Patient with Anemia

Anemia is the reduction of the red cell mass and hemoglobin concentration below normal levels resulting in impaired oxygen delivery to the tissues.

Pathophysiology Anemia develops when the need for red blood cells exceeds the productive capacity of the bone marrow. Three major factors, either individually or in combination, can cause anemia. They are 1) excessive blood loss due to hemorrhage, 2) increased destruction of red blood cells, and 3) bone marrow failure leading to decreased production of erythrocytes (Table 15.2). Since the principal function of the red blood cell is to transport oxygen to the tissues, anemia results in tissue hypoxia. Compensatory mechanisms responsible for improving oxygen transport include a reduction in the oxygen affinity of hemoglobin, increased stroke volume which increases cardiac output, decreased peripheral vascular resistance, decreased blood viscosity, regional redistribution of blood flow, and a decrease in circulatory time. In effect, a *hyperdynamic* circulatory state results. Progressive increase in the severity of anemia leads to circulatory congestion and fluid retention.

Clinical features The signs and symptoms associated with anemia, depend on its etiology, severity and rapidity of onset. Fatigue, headache, exertional dyspnea, palpitation, angina,[1] intermittent claudication are a few non specific presenting features of anemia.

A detailed history is necessary to pinpoint the cause of anemia. The diet taken by the patient — whether rich in iron, folate, vitamin B_{12}, protein and calories — should be assessed. Reports o 'pica'[2], a specific symptom of iron deficiency anemia or any blood loss like bleeding hemorrhoids or menorrhagia should be obtained, if any. Evidence pointing to hemolysis such as persistent jaundice, high-coloured urine gallstones and a requirement for blood transfusions should also be sought. A family history helps determine whether the blood disorder is inherited or not. A history of drug intake and exposure to toxins are important since they are an important cause o marrow suppression, of hemolysis and even blood loss, such as non-steroida antiinflammatory drugs.

A history of prolonged fever, bleeding tendency and progressive pallor is suggestive o bone marrow failure due to leukemia or bone marrow aplasia. The clinical history should include an enquiry regarding symptoms relating to renal dysfunction, thyroid dysfunction (hypothyroidism) and autoimmune disease. A review of previous hematological investigations and a history of blood transfusions help in assessing the onset as well as the severity o anemia. Pallor, the most important feature o

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[1] Usually in subjects with underlying coronary arter disease

[2] Pica (geophagia) is the habit of eating clay or mud

Table 15.2 Classification of anemia according to the mechanism of causation

I. Blood loss
- A. Acute: trauma
- B. Chronic: lesions of gastrointestinal tract, gynecologic disturbances

II. Increased rate of destruction (hemolytic anemias)
- A. Intrinsic (intracorpuscular) abnormalities of red cells

  Hereditary
  1. Red cell membrane disorders
     a. Disorders of membrane cytoskeleton: spherocytosis, elliptocytosis
     b. Disorders of lipid synthesis: selective increase in membrane lecithin
  2. Red cell enzyme deficiencies
     a. Glycolytic enzymes: pyruvate kinase deficiency, hexokinase deficiency
     b. Enzymes of hexose monophosphate shunt: G-6PD deficiency, glutathione synthetase deficiency
  3. Disorders of hemoglobin synthesis
     a. Deficient globin synthesis: thalassemia syndromes
     b. Structurally abnormal globin synthesis (hemoglobinopathies): sickle cell anemia, other unstable hemoglobins

  Acquired
  1. Membrane defect: paroxysmal nocturnal hemoglobinuria
- B. Extrinsic (extracorpuscular) abnormalities
  1. Antibody-mediated
     a. Isohemagglutinins: transfusion reactions, erythroblastosis fetalis
     b. Autoantibodies: idiopathic (primary), drug-associated, SLE, malignancies, mycoplasma infection
  2. Mechanical trauma to red cells
     a. Microangiopathic hemolytic anemias: thrombotic thrombocytopenic purpura, disseminated intravascular coagulation
     b. Cardiac prostheses
  3. Infections: malaria
  4. Chemical injury: lead poisoning
  5. Sequestration in mononuclear phagocytic system: hypersplenism

III. Impaired red cell production
- A. Disturbance of proliferation and differentiation of stem cells: aplastic anemia, anemia of renal failure, anemia of endocrine disorders
- B. Disturbance of proliferation and maturation of erythroblasts
  1. Defective DNA synthesis: deficiency or impaired utilisation of vitamin B_{12} and folic acid (megaloblastic anemias)
  2. Defective hemoglobin synthesis
     a. Deficient heme synthesis: iron deficiency
     b. Deficient globin synthesis: thalassemias
  3. Unknown or multiple mechanisms: sideroblastic anemia, anemia of chronic infections

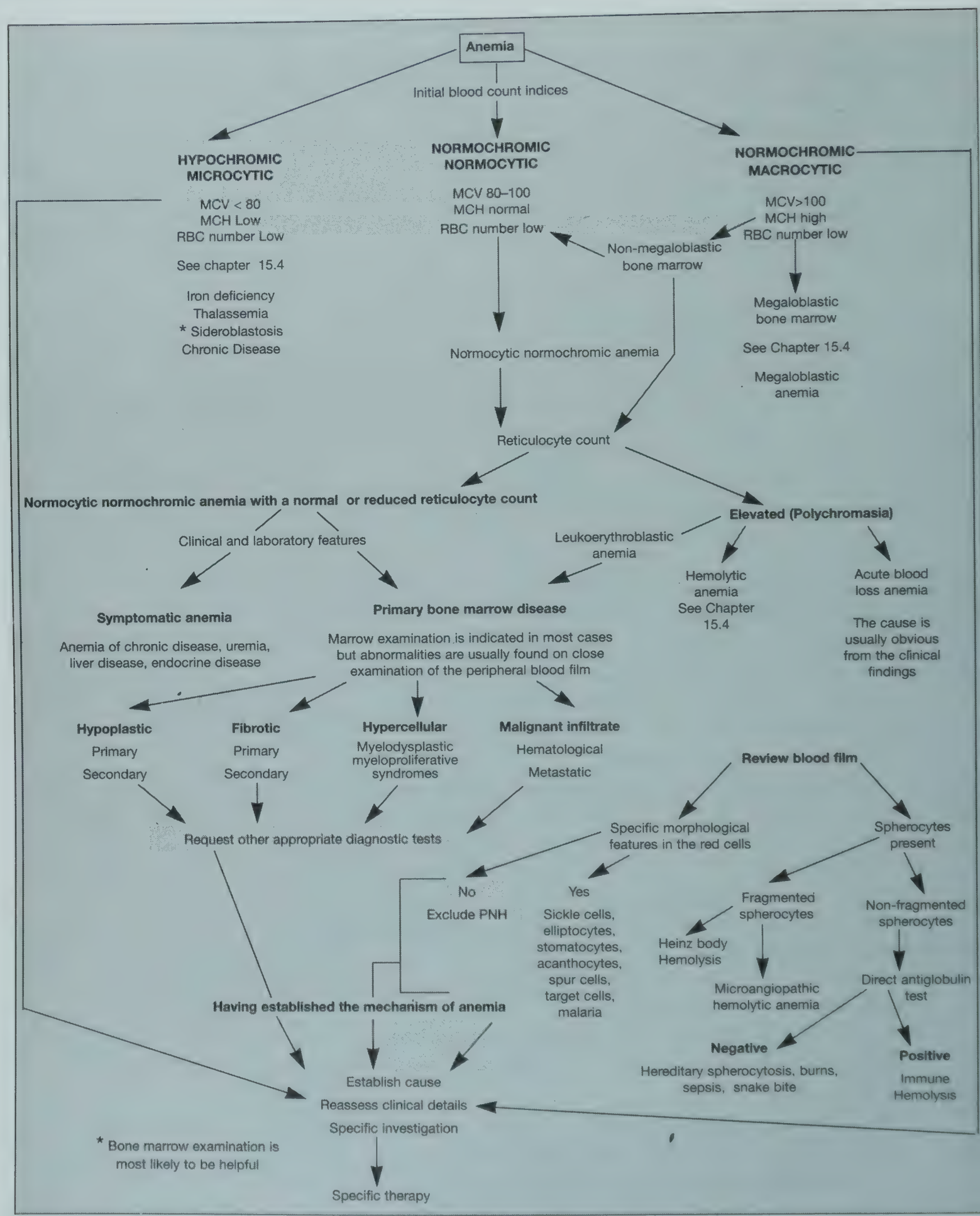


Table 15.3 The initial investigation of anemia

anemia, is better appreciated by examining the mucous membranes rather than by looking at the skin. Hyperkinetic circulation due to severe anemia manifests as a bounding pulse, a wide pulse pressure, accentuation of both heart sounds, and by the presence of a hemic murmur and a cervical venous hum. Tachycardia is not a feature of chronic anemia and usually occurs when acute anemia develops such as in states leading to rapid blood loss.

Presence of jaundice, petechiae, ecchymoses, glossitis, bone tenderness, lymphadenopathy, splenomegaly, hepatomegaly, chronic leg ulcers and neurologic abnormalities can also give a clue to the possible etiology of the anemia.

Investigations (Tables 15.3–15.5) Investigation in a patient with anemia include the following:

1. Hemogram which comprises of hemoglobin concentration, red blood cell count and hematocrit.

Table 15.4 Investigations in suspected hemolytic anemia

Peripheral smear morphology in hemolytic anemia

1. Spherocytes	-	congenital spherocytic anemia
	-	immune hemolysis
	-	extensive burns
	-	clostridial sepsis
	-	HbC disease
2. Stomatocyte		stomatocytosis
3. Ovalocytes		ovalocytosis
4. Schizocytes		red cell fragmentation syndromes
5. Sickle cells		sickle cell disease
6. Target cells		hemoglobinopathy (HbC, HbS), liver disease, thalassemia
7. Blister cells		G-6 PD deficiency
8. Burr cells		liver disease, pyruvate kinase deficiency
9. Agglutination		immune hemolysis

Other laboratory investigations of hemolysis

General tests	*Results*
1. Reticulocyte count	increase in hemolysis or hemorrhage
2. Haptoglobin, hemopexin	decrease in hemolysis
3. Plasma hemoglobin and urine hemosiderin	present in intravascular hemolysis
4. Chromium ^{51} red cell survival	reduced in all hemolytic anemia
5. Bilirubin	increased in all hemolytic anemias
6. LDH	
Specific tests	
1. Osmotic fragility	increased in spherocytic anemia, both hereditary and acquired (AIHA)
2. Direct Coomb's test	positive in immune hemolysis
3. Immune assays e.g., G-6 PD deficiency, pyruvate kinase deficiency	decreased activity
4. Hemoglobin electrophoresis	
• HbS, HbA_1	sickle cell disease
• HbA_2, HbF, HbA	thalassemia
• HAM or sugar water test	positive in PNH

Table 15.5 Laboratory parameters in hypochromic-microcytic anemia and disorders of iron metabolis

	Serum Fe	*TIBC*	*Transferrin saturation*	*Serum ferritin*	*Bone marrow stores*	*Sideroblasts*
Iron deficiency	↓	↑	↓	↓↓	absent	↓
Chronic disease/infection/ inflammatory disorders or malignancy	↓	N or ↓	↓	N or ↑	N or	↓
Sideroblastic anemia	N or ↑	N or ↓	N or ↑	↑	↑	Ring sideroblasts
Thalassemia	N or ↑	N or ↓	N or ↑	↑	↑	↑
Pregnancy	N or ↓	↑	↓	N or ↓	N or ↓	N
Hemochromatosis	↓	N or ↓	↑	↑↑↑	↑↑↑	N or ↑

TIBC = total iron binding capacity; ↑ = increase; ↓ = decrease; N = Normal

2. Red cell indices, that is, mean corpuscular volume (MCV), hemoglobin (MCH) mean corpusclular hemoglobin concentration (MCHC) and red cell distribution width (RDW)[1]. Of these, MCV is the most useful index. It helps to classify the anemia into the three essential types–normocytic, microcytic and macrocytic (Table 15.3).
3. A *reticulocyte count* reflects the erythropoietic activity of the bone marrow. Reticulocytes are large polychromatophilic red cells which have been prematurely released into the circulation before completion of hemoglobin synthesis. A normal reticulocyte count is less than one per cent of the total circulating red cell mass. Anemia causes tissue hypoxia, a potent stimulant of erythropoietin synthesis. The latter stimulates erythropoiesis. This results in an increased number of reticulocytes being thrown into the circulation. Therefore, a high reticulocyte count is a feature of the reactive bone marrow seen in hemolytic anemias, and a low reticulocyte count is encountered in anemia secondary to bone marrow failure syndromes.
4. Examination of a peripheral smear is of paramount importance in the evaluation of anemia. Abnormalities in red cell size and shape are the hallmark of hemolytic anemia (Table 15.4). *Oval-shaped red blood cells* are diagnostic of elliptocytosis. Red blood cells with a slit-like appearance (stoma, which replaces the central pallor), are seen in *stomatocytosis*. *Spherocytosis* is characterised by erythrocytes which appear smaller than the normal red cell but which lack the central pallor. When spherocytosis is seen in association with spontaneous agglutination of red cells autoimmune hemolytic anemia (AIHA) is a likely diagnostic possibility. It can be confirmed by performing a *Coomb's test*. A positive Coomb's test is a characteristic feature of AIHA. When a peripheral smear shows spherocytes but the direct Coomb's test is negative, the diagnosis is an inherited hemolytic disorder: congenital spherocytic anemia. Red cell fragments or *schizocytes* suggest that the hemolysis is due to intravascular pathology such as hemolysis

[1] Red cell distribution width in automated machines; this is a measure of variation in red cell size, i.e. anisocytosis. Normal value = 11.5–14.5 per cent.

secondary to vasculitis, cardiac valve abnormalities, disseminated intravascular coagulation or metastatic tumour deposits.

Sickle cells are diagnostic of sickle cell anemia. *Blister* or *bite cells* are characteristic of the hemolytic phase of G-6 PD deficiency. Severe anisocytosis with hypochromic *target cells* are specific for thalassemia major. MCV greater than 100 fl[1] with larger than normal RBCs in the peripheral smear is a feature of macrocytic anemia. Macrocytosis occurs not only in megaloblastic anemia but also in congenital dyserythropoietic anemias and chronic liver diseases. When MCV is less than 80 fl the red blood cell is described as a microcyte.

Hypochromic microcytosis is seen in iron deficiency anemia, congenital dyserythropoietic anemia, lead poisoning, chronic inflammatory diseases as well as in thalassemia trait. Serum ferritin is low in iron deficiency anemia but is normal in all the other conditions, thus differentiating iron deficiency anemia as a cause of hypochromic microcytic anemia (Table 15.5).

Normocytic anemia, when associated with blasts in the peripheral smear is diagnostic of a hematological malignancy. In the absence of blasts in the peripheral blood smear the cause of anemia can be determined by performing a reticulocyte count. If the reticulocyte count is low, a marrow study is mandatory. Occasionally anemia is the presenting feature of chronic renal failure. Renal function tests help in the diagnosis of the latter condition.

5. *Hemoglobin electrophoresis* gives confirmatory evidence regarding a specific hemoglobinopathy, such as sickle cell disease. An enzyme assay is necessary to establish the diagnosis of G-6 PD deficiency or pyruvate kinase deficiency.
6. *Bone marrow*: Anemia for which the diagnosis is not clear and pancytopenia with or without immature cells, are two conditions for which a bone marrow aspiration study is of help. *Generalised hypocellularity* is suggestive of a toxic injury to the bone marrow. Isolated hypoplasia of the erythroid precursors is often a feature of immunologic injury to the bone marrow. *Erythroid hyperplasia* occurs in hemolytic anemia. Hypercellularity with abnormal tumour or blast cells is seen in hematological and metastatic malignancies.

[1] fl=femtolitre, 10^{-15}L.

Management The treatment of anemia depends on the type of anemia.

Approach to a Patient with Bleeding Tendencies

A bleeding tendency is defined as bleeding due to a breakdown in hemostasis which is disproportionate to the degree of injury.

Pathophysiology As has been discussed earlier, normal hemostasis depends upon the proper functioning and interaction of platelets, the vascular endothelium and clotting factors. A bleeding tendency results from dysfunction of any of these three factors, or due to the excessive consumption of platelets and clotting factors, or may result from the abnormal activation of the fibrinolytic pathways.

Clinical approach

History (Table 15.6): Usually, a careful history and a meticulous clinical examination is adequate to pinpoint the diagnosis in a subject with a bleeding tendency. Firstly, one should ascertain whether the bleeding is due to a focal vascular lesion, that is, vessel wall disruption such as a bruise, or due to generalised vascular dysfunction resulting from a pathology involving the platelets or the coagulation factors. If it is due to the latter cause, it should be determined whether the bleeding tendency is a recent phenomenon or if it dated from early childhood (an inherited disorder presenting from early infancy or childhood). This is further corroborated by a positive family history. An acquired bleeding disorder, however, is of

recent onset and the family history is not suggestive of a hemorrhagic tendency. Platelet and vascular endothelial dysfunction manifest as skin bleeds, that is, petechiae or purpura, and mucosal bleeds (epistaxis and gum bleeds). The presence of widespread ecchymoses, intramuscular hematomas and hemarthroses points to coagulation factor deficiency. Hemorrhages within organs like the brain, the genitourinary tract and the gastrointestinal tract can occur due to severe dysfunction of platelets, vessel walls or clotting factor deficiencies. Similarly, prolonged bleeding following surgery, dental procedures and trauma can follow if there is dysfunction of any of the factors necessary for normal hemostasis. Bleeding occurs immediately after injury in vascular and platelet disorders, whereas it is delayed in coagulation factor deficiencies.

A history of simultaneous bleeding from multiple non-adjacent sites occurs in disorders concomitantly involving the vessel wall, the platelets and the coagulation factors, for example, thrombotic thrombocytopenic purpura (TTP) and disseminated intravascular coagulation (DIC). Usually an acquired bleeding disorder is associated with an underlying systemic illness. Symptoms suggestive of any malignancy, collagen vascular disorders, other autoimmune diseases, infections and renal failure should be sought in bleeds presumably related to a low platelet count.

Acquired coagulation factor deficiency disorders are often due to deficiency of vitamin K-dependent factors, a problem encountered in malabsorption syndromes and chronic liver disease (particularly those involving the biliary tree).

Drugs can adversely affect both the platelets and coagulation factors. Hence a careful history of all the medication taken by the patient is of great importance in the evaluation of a subject with bleeding tendencies.

Physical examination: This should include assessment of the site, size and extent of bleed. Presence of pallor, tachycardia, a feeble pulse

Table 15.6 Bleeding: platelet defects vs coagulation defects

Clinical approach	*Platelet/capillary defect*	*Coagulation factor defect*
1. Preceding injury		
A. None	Spontaneous bleeding from mucosa	Spontaneous bleeds into joint/muscle
B. Superficial cut	bleeding profuse, prolonged	minimal bleed
C. Deep cut	bleed controlled by application of pressure	poor response to pressure
D. Joint injury	rare	hemarthroses
E. Petechiae (1 mm size)	common	rare
Purpura (1 mm–1 cm)	common	rare
2. Investigations	BT prolonged	BT normal
	abnormal platelet count	increased PT increased APTT
	abnormal platelet function	normal platelet function

BT= bleeding time; APTT = activated partial thromboplastin time; PT = prothrombin time

and a low blood pressure indicate the severity of the bleed.

Hemarthroses is pathognomonic of hemophilia A and B. In acquired bleeding disorders, the physician should look for lymphadenopathy, hepatomegaly, splenomegaly, jaundice and ascites. Stigmata suggestive of collagen vascular disorders, chronic renal failure, liver failure and septicemia should also be sought. Massive hemangiomas often cause consumptive thrombocytopenia and their presence should not be ignored. A Hess test[1] can be conducted as part of the physical examination. In short, a thorough physical examination is of great importance in pinpointing the etiology of the bleed.

Investigations Baseline investigations in a subject with a bleeding tendency include estimation of platelet count, bleeding time (BT), prothrombin time (PT), activated partial thromboplastin time (APTT), and evaluation of a peripheral blood smear (Table 15.7). The bleeding time is prolonged beyond 10 minutes in disorders of platelets and the vascular endothelium.

A platelet count of less than 20,000/mm^3, is associated with spontaneous bleeds. Bleeding is uncommon when the platelet count exceeds 50,000/mm^3.

Abnormal platelet morphology, the presence of abnormal blasts and evidence of hemolysis can all be assessed by examination of a peripheral smear.

Coagulation function tests like PT, APTT are normal in platelet disorders. Further discussion of platelet function tests is beyond the scope of this text.

Prothrombin time exceeds 14 seconds in conditions affecting the extrinsic or the final common coagulation pathway, that is, in deficiencies of factor II, V, VII or X. The normal activated partial thromboplastin time (APTT) is 25–40 seconds. It is useful in assessing adequacy of factors XII, XI, IX, and VIII. APTT is prolonged in hemophilia A and B. Bleeding time and platelet count are normal in coagulation factor deficiencies.

[1] The Hess test is a measure of capillary fragility. An area 2.5 cm × 2.5 cm is marked out in the antecubital fossa. A sphygmomanometer cuff is inflated upto 80 mmHg for 5 minutes. Appearance of >5 petechiae after a further period of 5 minutes of observation is abnormal. The test has not been standardised.

Approach to a Patient with Lymphadenopathy

Lymphadenopathy is an abnormal increase in size of a lymph node with or without an alteration in its consistency.

Etiology Lymphadenopathy can be due to many causes. Enlarged lymph nodes may result from reticuloendothelial cell hyperplasia, inflammation, infiltration by neoplastic cells or due to extramedullary hematopoiesis. Presence of lipid-laden macrophages, as seen in storage disorders, is also a rare cause of lymphadenopathy. The causes of lymphadenopathy are shown in Table 15.8.

Clinical evaluation When a patient presents with enlarged lymph nodes, a physician's primary concern is to rule out the presence of a lymphoreticular malignancy or tuberculosis. A history of prolonged fever, weight loss, night sweats or lassitude may suggest tubercular lymphadenitis. Recent febrile illness may suggest *reactive hyperplasia* of lymph nodes. A history of local breach of skin with infection in the drainage areas of the lymph nodes suggests sepsis as a probable cause of lymphadenopathy. Pruritus, bleeding tendency or weight loss draws attention to the possibility of an underlying lymphoreticular malignancy. A history of sexual habits must also be obtained routinely. Occasionally, administration of sera or drugs (phenytoin sodium) can also lead to enlarged nodes and a detailed history about this should be sought. Physical examination includes evaluation of all lymph node regions and

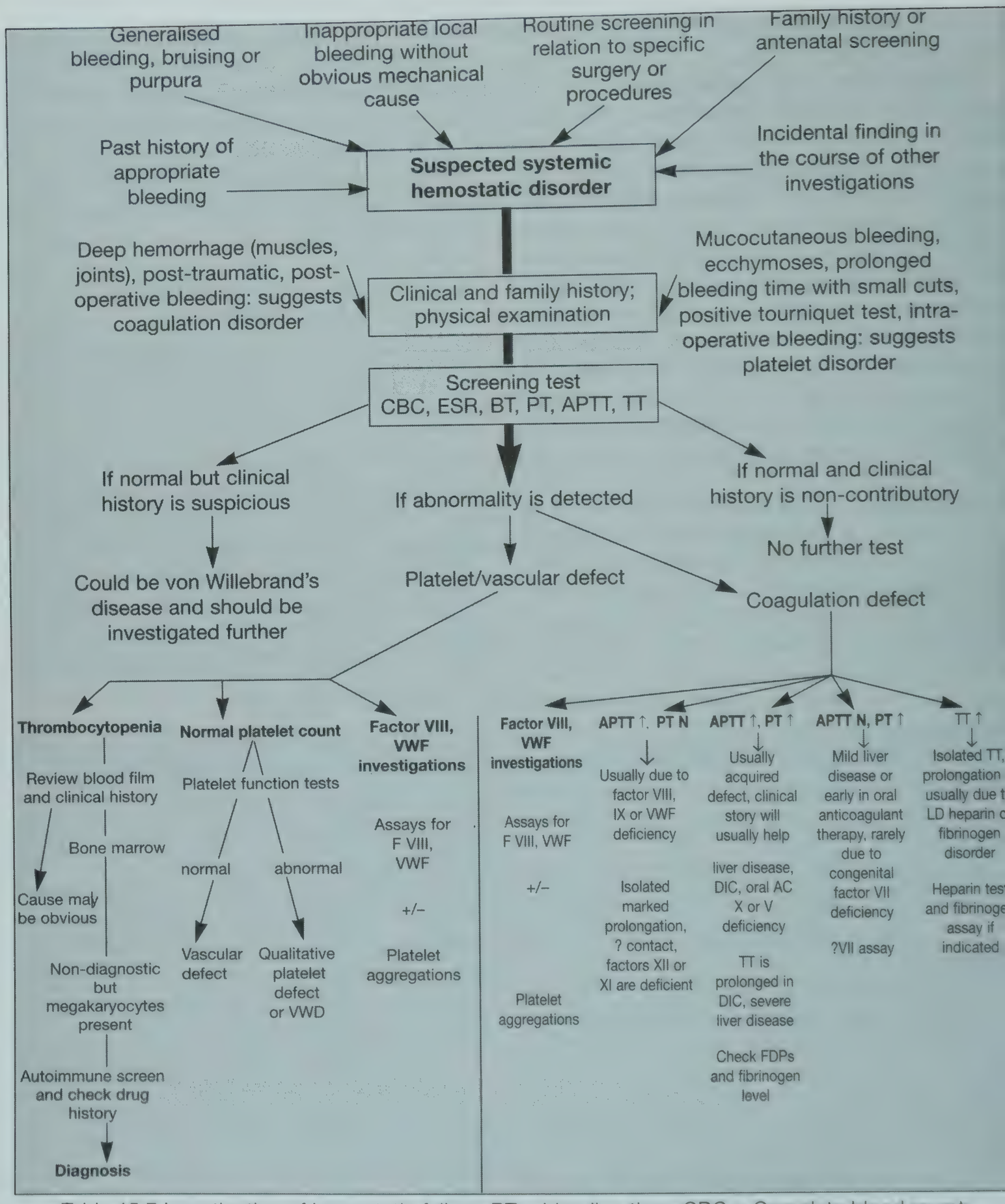


Table 15.7 Investigation of hemostatic failure: BT = bleeding time; CBC = Complete blood count; PT = prothrombin time; APTT = activated partial thromboplastin time; TT = thrombin time; N = normal; VWF = von Willebrand's factor; VWD = von Willebrand's disease; DIC = disseminated intravascular coagulation; AC = anticoagulants; FDP = fibrin degradation products; LD = low dose

Table 15.8 Causes of lymphadenopathy

A. **Infections**	
Bacterial	local infection with any pathogen
Mycobacterial	- tuberculosis
	- atypical mycobacteria (*M. scrofulaceum, M. avium*)
Spirochaete	syphilis
Chlamydia	lymphogranuloma venereum
Fungal	actinomycosis
Viral	- HIV
	- infectious mononucleosis
	- cytomegalovirus
Parasitic	- toxoplasmosis
B. **Malignancies**	
Solid tumours	
Cervical lymphadenopathy	head and neck cancers
Supraclavicular and scalene lymphadenopathy	GI and lung cancer
Axillary lymphadenopathy	breast cancer
Inguinal adenopathy	melanomas, superficial genital cancers
Lymphomas	
Leukemias	
C. **Miscellaneous**	
Sarcoidosis; phenytoin sodium (pseudolymphoma);	
Connective tissue disorders like SLE, rheumatoid arthritis; serum sickness	

evaluation for possible hepatomegaly or splenomegaly.

Localised lymphadenopathy: Tender lymph nodes indicate the presence of a focus of sepsis. 'Matted'[1] nodes are a feature of periadenitis[2] and are seen in both lymphomas and tubercular lymphadenitis. Draining sinuses, however, are a characteristic feature of tuberculous lymphadenitis. When the nodes are stony hard and fixed to the underlying tissue, secondary deposits are a strong possibility. The lymph nodes in Hodgkin's disease have beeen described as rubbery and the non-tender inguinal nodes of syphilis have a shotty consistency (firm like lead).

[1] Matted means adherent to one another.

[2] Periadenitis is the inflammation of the lymph node capsule with contiguous spread.

Cervical and supraclavicular lymphadenopathy: The head and neck should be carefully examined for malignant or septic foci. Tonsillitis or a carious tooth are some common infections causing enlarged anterior cervical nodes. Cervical adenopathy can also occur due to tuberculosis. The occipital lymph nodes are enlarged in pediculosis. Rubella infection and toxoplasmosis can cause enlarged posterior cervical lymph nodes.

Axillary and thoracic lymphadenopathy: Axillary lymphadenopathy necessitates a careful breast examination. Mediastinal lymphadenopathy usually represents tuberculosis, lymphoma or a metastatic carcinoma. Bilateral asymmetrical 'hilar adenopathy' is suggestive of pulmonary sarcoidosis. In children, a tubercular primary complex can manifest as mediastinal or

hilar lymphadenopathy.[1] Enlargement of inguinal lymph nodes is common among people who have a habit of walking with bare feet. A malignant focus in the drainage areas of the femoral and inguinal nodes can also result in their enlargement. Sexually transmitted diseases like syphilis, lymphogranuloma venereum (tender bubo) are important causes of inguinal lymphadenopathy. The absence of regional cutaneous or subcutaneous infective foci shou therefore alert the physician. Epitrochle lymph nodes may be enlarged in hand infectio (unilateral) or in lymphomas.

Generalised lymphadenopathy is a manifestati of systemic diseases such as lymphoreticul malignancies, AIDS, serum sickness or vi infections.

Investigations (Fig 15.4) As in any disord relating to the reticuloendothelial system, hemogram, peripheral blood smear study a

[1] Mediastinal and hilar adenopathy are more easily detected by the chest X-ray than clinically. Occasionally, they are benign and transient, the so-called *Castleman's disease.*

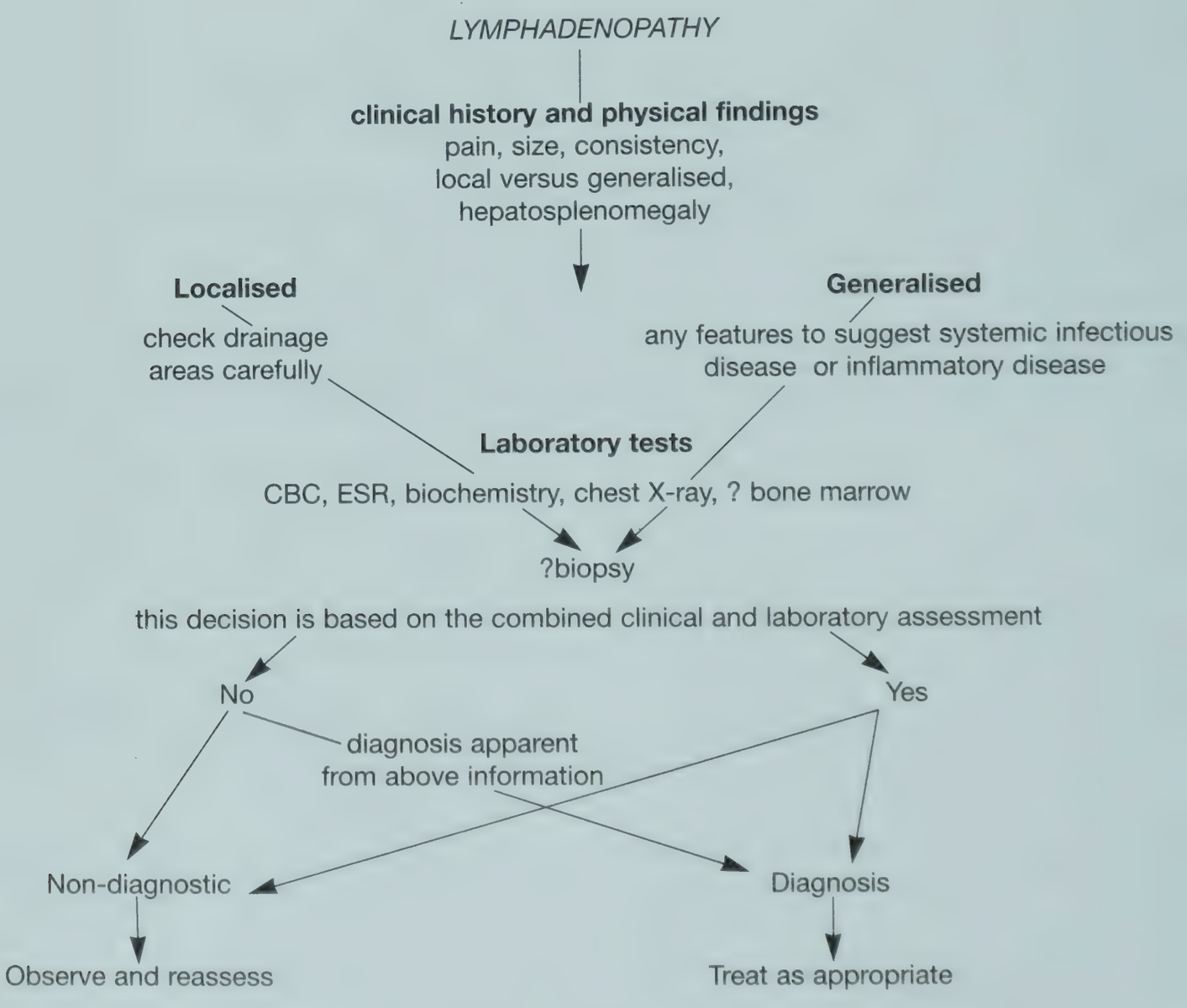


Fig 15.4 Investigation of lymphadenopathy: CBC = complete blood count; ESR = erythrocyte sedimentation rate

platelet count help in diagnosing hematological disorders causing lymphadenopathy. A Mantoux test, and sputum smear and culture for acid-fast bacilli may be obtained to diagnose pulmonary tuberculosis. Estimation of 'TORCH'[1] titres, Epstein-Barr, virus serology or HIV antibody titres are other useful tests in investigating the cause of lymphadenopathy. A lymph node aspirate often provides cytologic evidence of tuberculosis (caseating granuloma), or of a malignancy. If the lymph node aspirate is negative, a lymph node often provides confirmatory evidence in tuberculosis and in lympho-proliferative diseases. A bone marrow biopsy must be considered if there is strong suspicion of a hematologic malignancy and the lymph node biopsy is unrevealing. Abdominal ultrasonography and CT scans are helpful in staging lymph node malignancies but do not provide a tissue diagnosis. CT-guided needle aspiration of abdominal lymph nodes or a 'mini laparotomy' may provide a tissue diagnosis in these cases.

Approach to a Patient with Splenomegaly

The spleen under normal circumstances is not palpable. It has to enlarge to at least two and a half times its normal size before it becomes clinically palpable in the adult.

Etiology An increase in the splenic size can be due to various causes. Persistent venous congestion, either due to elevated pressure in the portal venous system or due to right heart failure results in congestive splenomegaly. Reticuloendothelial cell hyperplasia within the spleen occurs as a reaction of the body to infections like typhoid, malaria, kala azar and tuberculosis. Chronic immunoinflammatory conditions like systemic lupus erythematosus are also a cause of splenomegaly. Infiltration by malignant cells of myeloid or lymphoid origin can lead to massive splenomegaly. When the spleen develops foci of extramedullary hematopoiesis (as in myelofibrosis or myeloid metaplasia), massive splenomegaly can result. Rarely, the spleen can be massively enlarged in storage disorders where the splenic macrophages become laden with complex lipids.

Clinical approach (Fig 15.5)

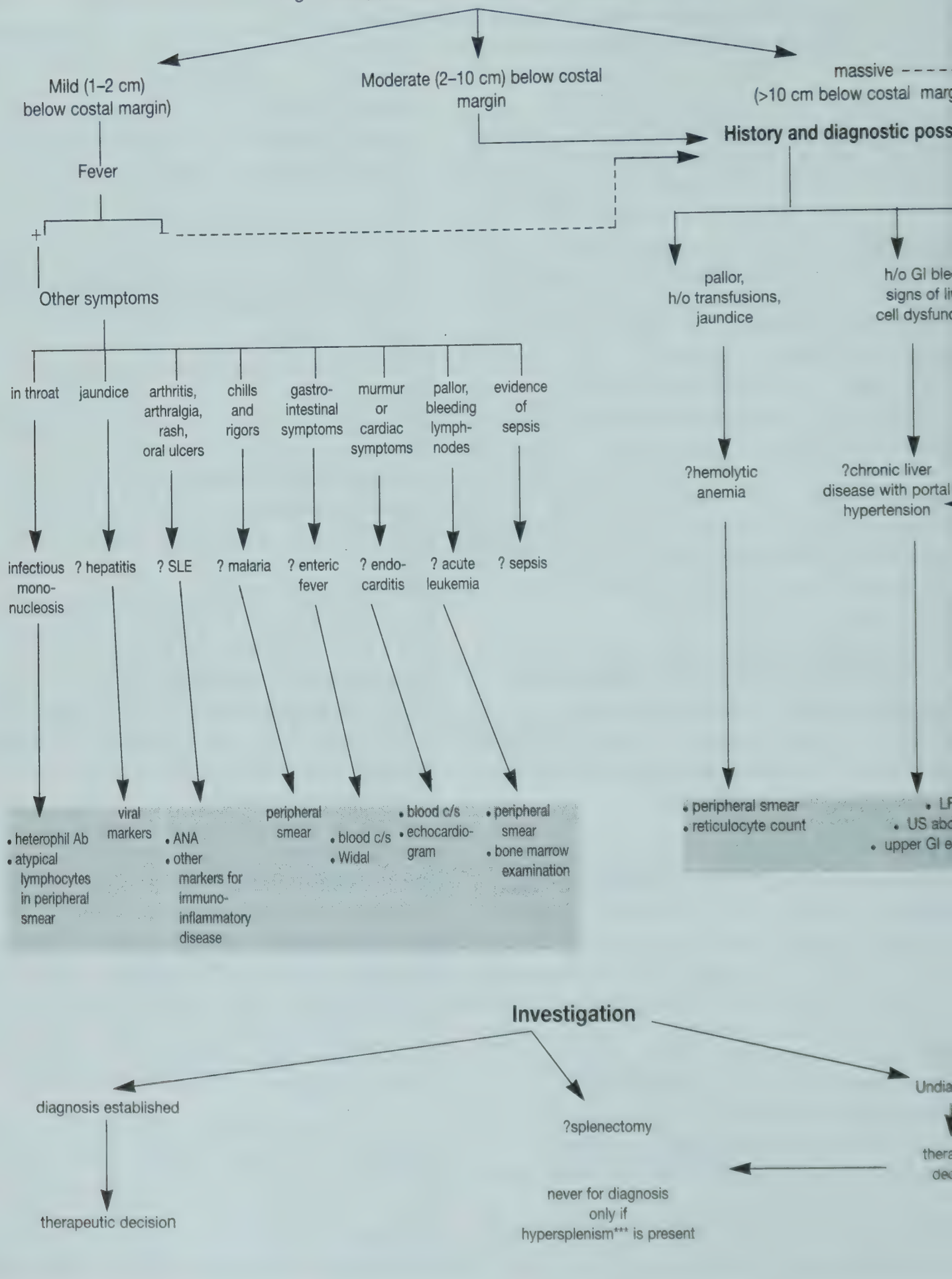
History: A history of fever is of great importance in the evaluation of splenomegaly. Presence of continuous or spiking fever with chills of recent origin is suggestive of an infective cause. A history of prolonged fever, weight loss, fatigue, night sweats or pruritus indicates a more ominous illness such as a lymphoid malignancy. Fever associated with joint symptoms, renal and hematological involvement are often a feature of immunoinflammatory diseases like SLE. If fever is not the presenting feature, a history of jaundice, alcoholism, upper or lower gastrointestinal bleeding would lead one to think of the possibility of congestive splenomegaly secondary to chronic liver disease and portal hypertension. Progressive pallor, gallstones, requirement of periodic blood transfusions and a family history of a similar illness are important clues to the possibility that splenomegaly is due to a hemolytic anemia.

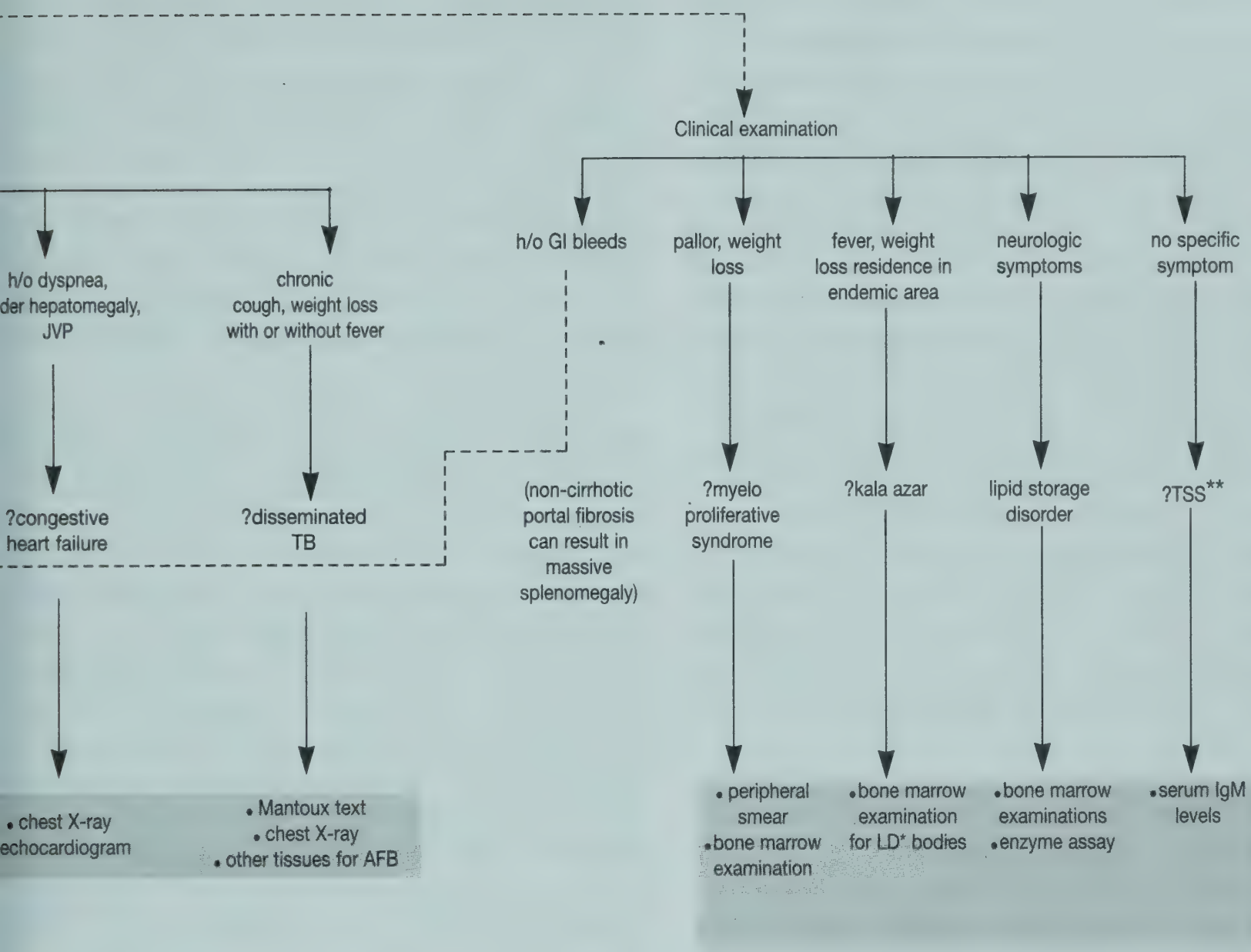
History of exertional dyspnea, angina, syncope, rheumatic heart disease or congenital heart disease indicate that the splenomegaly probably results from cardiac failure. In these situations, splenomegaly is invariably associated with the murmur of tricuspid regurgitation, elevated jugular venous pressure and a pulsatile liver. Developmental delay, 'fits' and blindness often indicate that a storage disorder is the cause of splenomegaly.

Physical examination: This should include assessment for the presence of anemia, jaundice, other signs of liver cell failure, lymphadenopathy, hepatomegaly, bleeding tendencies (petechiae and purpura), joint swellings, bone tenderness and ascites. The cardiovascular

[1] TORCH stands for 'Toxoplasmosis, Rubella, Cytomegalovirus and Herpes' all of which can cause lymphadenopathy.

Fig 15.5 **Approach to a patient with splenomegaly**





* LD bodies : Leishman-Donovan bodies
** TSS : Tropical splenomegaly syndrome
*** Hypersplenism : i) presence of large spleen
ii) decrease in count of two out of three cell types

system must be examined to exclude right-sided congestive heart failure. A thorough neurological evaluation, including examination of the fundus is essential when the possibility of a lipid- or glycogen-storage disorder is considered.

It is useful in clinical practice to assess the size of the spleen and classify it as *mild* (just palpable 1–2 cm below the left costal margin correlating with a splenic weight of less than 500 grams), *moderately palpable* (3–10 cm below the left costal margin, correlating with a splenic weight of 500–1000 grams) and *massively palpable* (beyond the umbilicus, correlating with a splenic weight of more than 1000 grams).

A small spleen is a feature of infective disorders such as typhoid, acute malaria, infectious mononucleosis, sepsis, infective hepatitis, disseminated tuberculosis and infective endocarditis. It can also be a feature of systemic lupus erythematosus. Hemolytic anemia, acute leukemia and congestive splenomegaly due to portal hypertension often present with moderate splenomegaly. Massive splenomegaly is a characteristic feature of chronic myeloproliferative disorders (chronic myeloid leukemia, myelofibrosis), chronic lymphoproliferative disorders (chronic lymphyocytic leukemia, hairy cell leukemia), lymphomas, histiocytosis, chronic malaria, kala azar and Gaucher's disease (storage disorder). A large spleen is also seen in the tropical splenomegaly syndrome (TSS), a disease characterised by abnormal immune response to malarial antigens.

Investigations A baseline hemogram (which includes a hemoglobin, hematocrit, MCV, MCH, MCHC, reticulocyte count, platelet count and a peripheral smear examination) gives valuable information regarding the possibility of various hematological disorders. It also helps to diagnose malaria. A Mantoux test, chest X-ray, sputum examination for acid-fast bacilli, Widal test, blood cultures and heterophil antibody titres are necessary when infectious disorders are a possibility.

Liver function tests, abdominal ultrasonograms and an upper gastrointestinal endoscopic examination are essential in the evaluation of chronic liver disease as a cause of splenomegaly. In suspected connective tissue disorders, rheumatoid factor and antinuclear antibody assays are performed. IgM levels are elevated in the tropical splenomegaly syndrome. Confirmatory evidence of disorders such as malignancy, storage diseases and myelofibrosis is sought by examination of the bone marrow aspirate. Bone marrow examination helps to diagnose infective disorders like typhoid (bone marrow culture is useful in this condition), malaria and kala azar (diagnosed by the presence of LD bodies), when evidence of these infections are not obtained from other investigations.

KEY CONCEPTS

Anemia

- Anemia may be due to decreased production of blood, increased destruction of blood components, or due to blood loss.
- Symptoms depend on the degree of anemia and the rapidity of its development. Symptoms are generally non-specific.
- Physical examination findings include conjunctival and mucosal pallor (pallor of palm creases suggests Hb<7g/dl). Signs of a high cardiac output (wide pulse pressure, a precordial systolic flow murmur) appear when anemia is severe (Hb< 7.5 g/dl). Koilonychia is seen in severe iron deficiency; glossitis is seen in both iron deficiency and vitamin B_{12} deficiency. Jaundice, splenomegaly, leg ulcers, and a family history of similar disease are suggestive of a hereditary hemolytic anemia. Presence of bone pain, lymphadenopathy, hepatosplenomegaly, bleeding and frequent infections points to the possibility of a neoplastic process involving the bone marrow or lymph nodes.
- The peripheral blood smear examination provides a simple approach to anemia; anemia may be microcytic hypochromic, normocytic normochromic, or macrocytic.
- Microcytic hypochromic picture suggests a production defect due to abnormal heme (iron deficiency), porphyrin (sideroblastic anemia) or globin synthesis (thalassemia). Important investigations which help distinguish these entities include serum ferritin, TIBC, and bone marrow iron stores.
- A normocytic normochromic picture suggests increased destruction or reduced production (hypoplasia). Causes include hemorrhage, chronic hemolysis, aplastic anemia, chronic inflammatory conditions, and neoplastic infiltration of the marrow. Tests of hemolysis (increased bilirubin, increased urinary urobilinogen, reduced haptoglobin, ^{51}Cr labelled RBC survival, Coomb's test) and a bone marrow examination help distinguish these conditions.
- A macrocytic anemia may be due to megaloblastic anemia, alcoholism, liver disease or hypothyroidism. Investigations include serum and red blood cell folate and B_{12} levels, the Schilling test (for pernicious anemia), liver function tests, thyroid function tests and bone marrow examination.
- Treatment of anemia depends on the underlying etiology.

Bleeding tendency

- Hemostasis after an injury requires the formation of a stable hemostatic plug; this requires integrity of the vascular and tissue components, the platelets and the coagulation proteins. Increased bleeding may be due a defect of any one of these components (*vascular dysfunction:* autoimmune purpura, scurvy, telangiectasia, paraproteinemia, senile purpura; *platelet dysfunction:* thrombocytopenia thrombocytopathia (intact number but abnormal function); coagulation factor deficiency hemophilia, von Willebrand's disease, DIC, liver disease).
- A careful history often provides valuable clues to the likely etiology. A history of bleeding which is immediate and mucocutaneous in location suggests a platelet or vascular etiology. When bleeding is delayed and deep-seated, a coagulation factor deficiency is likely. A family history of disease and an onset from childhood suggest a hereditary condition (e.g., hemophilia, von Willebrand's disease) while a history of onset after use of drugs (as in drug-induced thrombocytopenia) suggests an acquired cause.
- Physical examination also yields important clues. Mucocutaneous petechiae suggest platelet dysfunction while hematomas and hemarthroses suggest a coagulation factor deficiency.
- A combined interpretation of the platelet count, BT, APTT and PT often suggests the diagnosis. A reduced platelet count with a prolonged BT suggests thrombocytopenia, whereas a normal platelet count in the face of a prolonged BT suggests thrombocytopathy. A normal platelet count and BT with a prolonged PTT but normal PT suggest an *intrinsic pathway defect* (hemophilia A or B). A normal plataelet count, BT, PTT with a prolonged PT suggest a *defect of the extrinsic pathway* (factor VII deficiency). A normal platelet count with a prolonged BT and PTT (but normal PT) is encountered in von Willebrand's disease. When several of these parameters are abnormal, a condition like DIC should be suspected. When all these parameters are normal but the patient has purpura, a vascular cause is likely.
- Treatment depends on the etiology of the bleeding tendency.

Lymphadenopathy

- While evaluating a patient with lymphadenopathy, attention to the age of the patient, the location (localised versus generalised), characteristics of the swelling and the clinical setting provide valuable clues.
- Most adults have a few small firm cervical or inguinal lymph nodes which do not change over time and which do not indicate any disease or merit any investigation.

Children also exhibit physiologic hypertrophy of lymphoid tissue during certain phases of growth.

➢ Localised lymphadenopathy is often due to an infection or a tumour in the area of the drainage of the lymph nodes. Thus, infections which can cause localised lymphadenopathy include anterior cervical: streptococci, tuberculosis and atypical mycobacteria; posterior cervical: rubella, toxoplasmosis; occipital: pediculosis; genital: plague, LGV, chancroid, primary syphilis, donovanosis. Palpable supraclavicular lymph nodes must lead to a search for a neoplasm in the GI tract, while palpable axillary lymph nodes must necessitate a careful breast examination.

➢ The consistency and character of the nodes may yield some clues. Infective adenopathy is often tender, and the skin over it may be inflamed; sinus formation is usual with tubercular lymphadenitis as is a matted appearance. The lymph nodes in Hodgkin's disease are rubbery and non-tender, while those of syphilis are shotty (lead-like) and non-tender. Stony hard lymph nodes often harbour metastatic disease.

➢ The physical examination must include a careful examination of the drainage area of the lymph glands. A peripheral blood smear, hemogram, chest X-ray and serology are useful investigations. Fine needle aspiration cytology or a biopsy of the lymph node yields a tissue diagnosis.

Splenomegaly

➢ A palpable spleen indicates an organ which is at least 2.5 times its normal size.

➢ Causes of splenomegaly include infections (acute: enteric fever, malaria, infective endocarditis, infectious mononucleosis, hepatitis; chronic: malaria, tuberculosis, kala azar), infiltrative diseases (lipid storage disease, sarcoid, amyloidosis, myeloproliferative syndromes (CML, PRV, myeloid metaplasia) and lymphoreticular neoplasms (leukemia, lymphoma), hemolytic anemia (especially hereditary forms like hereditary spherocytosis, thalassemia, red cell enzymopathies), congestive splenomegaly (portal hypertension, congestive heart failure) and immuno-inflammatory disease (SLE, rheumatoid arthritis [Felty syndrome]).

➢ History and physical examination yield important clues to the etiology of splenomegaly. A history of high fever suggests an infective etiology while a history of associated joint pains may suggest an immuno-inflammatory disease. History of jaundice, alcohol intake or a prior episode of GI bleeding points to the likelihood of portal hypertension. Exertional dyspnea, pedal edema and other cardiac symptoms may suggest congestive splenomegaly. A family history of similar disease and an association with pallor, leg ulcers and gallstones suggest a hemolytic anemia. If there is a history of developmental delay and there are prominent neurologic findings, a lipid storage disorder is likely.

➢ The size of the spleen may also provide clues to the possible etiology. Massive splenomegaly is seen in CML, myelofibrosis, kala azar or portal hypertension and hemolytic anemia.

➢ Investigations include a hemogram (smear for malarial parasite if indicated), liver function tests, ultrasound (portal vein and hepatic vein patency), endoscopy (for varices), and bone marrow biopsy (for hematologic malignancies and storage disease).

➢ Treatment depends on the underlying cause of splenomegaly.

15.3 Diagnostic methods in hematologic disease

The Peripheral Blood Smear

The examination of the peripheral blood smear is the most important investigation in the evaluation of hematological disorders.

The manual method for making a peripheral smear is discussed here. Two clean glass slides are used: one is the spreader slide and the other is the slide on which the smear is made. A drop of blood from the finger is placed on the slide without touching the skin of the pricked finger. The drop is placed 1 cm from the edge of the slide. The left edges of the slide with the blood drop are held with the thumb and index finger of the left hand. With the right hand, the spreader slide is held at an angle of 45 degrees in front of the drop of blood. The spreader slide is then drawn towards the drop of blood and as soon as the two slides come into contact, the blood begins to spread along the edges of the angled slide. While still retaining the spreader slide at an angle of 45 and with its edge firmly against the horizontal slide, the spreader slide is rapidly pushed over the entire length of the slide. Thus, a smear 3–4 cm long is made. The ideal thickness of the film is such that there is some overlap of red cells throughout. The smear has a *'thick end'* and a *'thin tail'*.

Leishman stain The blood film prepared as above is air-dried. Then it is flooded with the Leishman stain and left aside for two minutes. Water in a proportion double the Leishman stain is then added on to the slide. After a period of five to seven minutes the slide is washed in a stream of buffered water until it acquires a pinkish tinge. The back of the slide is wiped clean and it is kept upright to dry.

The stained blood film is examined by placing a drop of oil on the slide and viewing it with the help of an oil immersion objective of a microscope. The portion of the smear where there is only slight overlapping of the red cells is chosen and the slide is examined. Each white cell seen is counted and recorded on a differential counter, for the count of 100 cells. Nucleated RBCs are enumerated separately. Automatic electronic counting of different cells (Coulter counters) can also be used for this purpose.

The RBCs are examined for their size, shape, hemoglobin content, immaturity, and for the presence of inclusion bodies or parasites.

Red blood cell morphology and number

Increased variation in size and shape of RBCs is referred to as anisocytosis and poikilocytosis. It may be due to the presence of RBCs larger than normal (*macrocytosis*), as seen in megaloblastic anemias, aplastic anemia, dyserythropoietic anemias and chronic liver disease. *Microcytosis*, (RBC is smaller than normal) is seen in iron deficiency anemia, thalassemia, lead poisoning and pyridoxine deficiency. Peculiar-shaped RBCs characteristic of specific hemolytic anemias, such as spherocytes, elliptocytes, stomatocytes and sickle cells can also be demonstrated in the peripheral smear. *Tear drops cells* are suggestive of myelophthisic anemias, while 'fragmented' RBCs and 'helmet'

cells are seen in microangiopathic hemolytic anemias. These terms are discussed in detail elsewhere.

Erythroblastemia refers to the presence of nucleated RBCs in the peripheral smear of normal newborn babies. They are also seen in disease conditions such as leukemias, myelofibrosis and extramedullary erythropoiesis.

Granulocyte morphology and numbers

An increase in WBC number (leukocytosis; >10,000/mm^3) occurs in a wide variety of inflammatory states. The type of white blood cell affected varies with the underlying cause. Pyogenic infections, tissue necrosis resulting from myocardial infarction, or burns manifest with *neutrophilic leukocytosis*. In severe sepsis, morphologic changes accompany the increase in number of neutrophils. Vacuolated cytoplasm, presence of toxic granules (coarser and more darkly staining than normal neutrophilic granules) and Dohle bodies (pale blue, round inclusions 2–3 μm in size in the periphery of the cytoplasm) are seen in severe sepsis. Presence of white blood cells with unsegmented nuclei in the peripheral smear indicates a *shift to the left* characteristic of severe infections. An abnormally low white blood cell count (leucopenia; <4000/mm^3) may occur because of a decrease in any one of the specific types of leukocytes. *Neutropenia* (<2500/mm^3) is the most common cause of a low white cell count and occurs following the intake of certain drugs, or as a part of failure of the bone marrow function or due to an accelerated immune-mediated destruction of WBCs.

Eosinophilic leukocytosis (>400/mm^3) is characteristic of allergic disorders such as bronchial asthma, eczema, pemphigus vulgaris, parasitic infections or the condition of 'tropical eosinophilia'. *Basophilic leukocytosis* (>100/mm^3) occurs in chronic myeloid leukemia, Hodgkin's lymphoma, chronic hemolytic anemias in bone marrow and graft rejections. *Lymphocytosis* (>4000/mm^3) is common in chronic inflammatory diseases such as tuberculosis, and brucellosis. It is also seen in acute viral infections and in pertussis. *Lymphopenia* (<1500/mm^3) occurs in viral infections, AIDS, lymphomas or with corticosteriod treatment.

Elevation in monocyte count (*monocytosis*; > 800/mm^3) is also encountered in chronic inflammation, such as tuberculosis, brucellosis, infective endocarditis, malaria and kala azar. Systemic lupus erythematosus, rheumatoid arthritis and inflammatory bowel diseases are non-infective causes of monocytosis.

Platelet morphology and number

Normally clumps of 8–20 platelets are seen per high power field of the blood smear. They are about 3–5 μm in diameter. *Giant platelets* (upto 7 μm) are a feature of thrombocythemia or myelofibrosis. In a rare inherited disorder (*Glanzman's disease*) platelets are singly arranged due to a failure in clumping.

Preparation and Evaluation of Bone Marrow Films

The technique of bone marrow aspiration is described in Appendix A. A large drop of marrow fluid is applied to each of 8–10 slides. The excess blood present in the marrow fluid is aspirated by using a 21 gauge needle to which a syringe is attached for the purpose. The film is made as described earlier, and is air-dried and stained. The staining time is double that required for a peripheral blood smear.

A well-spread bone marrow smear consists of a series of trails of marrow cells each leading upto a marrow fragment. A systematic examination requires a stepwise approach.

A careful examination is made of:

1. the number of marrow fragments: The fragments are few in number in a hypoplastic marrow and numerous in a hypercellular marrow.
2. marrow cellularity: The individual marrow fragments are examined to assess the

proportion of fat cells in it. In a normal fragment, fat cells constitute less than 50 per cent of the total number of cells. In hyperplastic fragments, the fat cells are absent. On the contrary, hypoplastic fragments contain a far greater proportion of fat cells than normal.

3. cellularity of the trails: The trails are hyper- or hypocellular depending on the cellularity of the marrow fragments.
4. erythropoiesis: Erythroblasts are arranged in clumps. Their activity is assessed by their number, maturity and type as normoblasts or megaloblasts Megakaryocytes are assessed for their number and the presence or absence of platelet formation is noted.
5. Leukopoiesis:
   The number and maturity of the white blood cell precusors is assessed. Abnormalities in morphology, such as the presence of phagocytosed inclusions or toxic granules is noted. The normal myeloid: erythroid ratio is 3–4: 1 and is determined by counting 200–500 cells.
6. Inclusions and iron contents:
   Malarial parasites, Donovan bodies, acid-fast bacilli and histoplasma infection can all be demonstrated in the bone marrow. Existence of abnormal storage cells characteristic of Gaucher's and Niemann-Pick's disease can also be identified. The iron content of the marrow is evaluated using Prussian Blue stain; marrow iron is absent in iron deficiency anemia and is increased in hemochromatosis, chronic inflammatory diseases and congenital dyserythropoietic anemias.

Investigation of a Bleeding Disorder

Since acute hemostatic failure is an emergency, simple, reliable, quick baseline investigations are necessary to pinpoint the cause, so that corrective measures can be taken promptly.

Thrombin time (TT)

TT is based on the principle that when thrombin is added to the plasma it will clot within 15–20 seconds in the presence of an adequate amount of fibrinogen in plasma. Thrombin time is abnormally prolonged in

1. dysfibrinogenemia,
2. hypofibrinogenemia due to either disseminated intravascular coagulation (DIC) or due to an inherited deficiency of fibrinogen, and
3. presence of inhibitory substances such as fibrin degradation products and heparin.

One stage prothrombin time (Quick's test)

This test measures the time taken for plasma to clot in the presence of tissue thromboplastin and calcium. Prothrombin time (PT) assesses the adequacy of factors II, V, VII and X in plasma. Normal prothrombin time is 12–14 seconds. Common causes of prolonged PT are obstructive liver disease, vitamin deficiency states, DIC, intake of oral anticoagulants and inherited deficiencies of factors V, VII, X or prothrombin.

Partial thromboplastin time with kaolin (PTT)

This test is also known as activated partial thromboplastin time (APTT). It measures the time taken for plasma to clot after activation by a contact factor such as kaolin, but without the addition of tissue thromboplastin. It assesses the efficiency of the intrinsic and the common pathway, that is, factors VIII, IX, V, X prothrombin and fibrinogen.

Platelet-poor plasma of the patient is added to a suspension of phospholipid and kaolin. Calcium is also added to the mixture. The time taken for this to clot is normally 30–40 seconds. It is prolonged in hemophilia A and B, DIC, liver disease, vitamin K deficiency, administration of heparin and in the presence of a circulating anticoagulant.

When APTT is prolonged the factor responsible can be identified by the following method. Normal plasma absorbed with barium sulphate retains factors VIII and IX. Normal

serum contains factors IX and XI. When the abnormal APTT is corrected by addition of adsorbed plasma and not by serum, factor VIII deficiency is present. If the abnormal result is corrected by serum and not by adsorbed plasma, the presence of factor XI deficiency is proven. If both the serum and adsorbed plasma correct the prolongation of APTT, factor IX deficiency is the possible cause.

Bleeding time

Bleeding time can be quantified by the standardised template method. A BP cuff is placed around the patients's arm above the elbow and inflated to a cuff pressure of 40 mmHg. The volar surface of the arm is cleaned and a sterile template is used to make linear slit about 7–8 mm long. The oozing is blotted with a filter paper at 15 second intervals. Bleeding ceases within 2.5–9.5 minutes in mos normal subjects.

A prolonged bleeding time is due t thrombocytopenia (platelet count <50,000/mm^3 disorders of platelet function, von Willebrand disease, vasculitis or in severe deficiencies o coagulation factors V and XI.

Accurate platelet count is now possible usin the electronic counter. Thrombocytopeni causes an abnormal bleeding time but TT, P and APTT are normal. Tests for platele function can be referred to in standar hematology laboratory manuals. These includ tests of platelet 'adhesion',[1] tests of platele 'aggregation' and tests of platele 'degranulation'.

[1] Adhesion refers to contact with a surface, whereas 'aggregation' refers to clumping of platelets with each other.

KEY CONCEPTS

Peripheral blood smear

➢ Evaluation of a PBS involves assessment of erythrocyte, WBC, and platelet counts along with an examination of erythrocyte morphology and WBC differential count.

RBC morphology

➢ *Microcytosis* is an RBC volume <80 fl. It is seen in iron deficiency thalassemia and sideroblastic anemia.

➢ *Macrocytosis* is an RBC volume >100 fl; it is seen in vitamin B_{12} folate deficiency, alcoholism and liver disease.

➢ Hypochromia refers to red cells with less than a normal amount of Hb (MCHC <30g/dl); it is typical of iron deficiency anemia.

➢ *Polychromasia* is a bluish tinge to red cells in the smear and is due to the presence of relatively immature erythroblasts. Along with reticulocytosis, it suggests a hemolytic state.

➢ Nucleated RBCs indicate overactive erythropoiesis (as in leukemia, marrow infiltration).

➢ Anisocytosis (variation in size) and poikilocytosis (variation in shape) are common in hemolytic states.

➢ *Heinz bodies* (denatured Hb) are seen in G-6PD deficiency. *Target cells* (central staining with a ring of pallor) are seen in thalassemia, liver disease, HbC, and uremia. *Howell-Jolly* bodies (nuclear remnants) are seen in post-splenectomy states, in leukemia and in magaloblastic anemia.

➢ Elliptocytosis, ovalocytosis, spherocytosis refer to morphologic abnormalities of RBC shape seen in corresponding hereditary conditions. *Schistocytes* (fragmented cells) are seen in DIC, prosthetic valves and indicate traumatic hemolysis.

WBC count and morphology

➢ A *shift to the left* indicates increased number of immature WBCs (as in infections) while a *shift to the right* indicates hypersegmented polymorphonuclear leucocytes (megaloblastic anemia, uremia, liver disease).

➢ Leucocytosis (>11.0 x 10^9/L) suggests pyogenic infection, a leukemoid reaction or a leukemia. Leucopenia (<3.0 x 10^9/L) may be seen in tuberculosis, typhoid, kala azar, viral infections, immunoinflammatory diseases, drug use, and in overwhelming bacterial infections.

➢ *Monocytosis* is seen in tuberculosis, malaria, kala azar, and viral infections (infectious

mononucleosis). *Eosinophilia* is seen in allergic diseases, parasitic infections, drug reactions, skin diseases, Addison's disease, certain types of leukemia and some types of vasculitis. Basophilia is usually indicative of a myeloproliferative disease. A leucoerythroblastic picture (presence of immature red and white cell precursors) is usually seen in infiltrative marrow disorders.

➢ Thrombocytopenia is a platelet count of $<150 \times 10^9$/L whereas a count of $>350 \times 10^9$/L denotes thrombocytosis.

Tests of blood coagulation

➢ *Bleeding time* (normal 7.5 minutes) is a good screening test for adequacy of formation of the hemostatic plug.

➢ *Activated partial thromboplastin* time (APTT; normal 30–40 seconds) is a screening test for clotting factors involved when coagulation is initiated by the intrinsic pathway (factors V, VIII, IX, X, XI, XII, prothrombin, fibrinogen). *Prothrombin time* (PT; normal is 11–14 seconds: >2 seconds more than control for a laboratory is abnormal) is a screening test for clotting factors involved when the extrinsic pathway is involved (factors V, VIII, X, prothrombin, fibrinogen).

➢ *Thrombin time* (TT; 12–20 seconds) is a screening test for the prothrombin-fibrinogen interaction.

Other hematologic investigations

➢ Bone marrow aspiration and biopsy are vital tests for differentiating among the various diseases which can produce a similar clinical picture or similar peripheral smear appearance. Bone marrow examination is essential for the diagnosis of leukemia and for investigating the patient with pancytopenia or thrombocytopenia. Bone marrow examination includes assessment of the cellularity, the myeloid/erythroid ratio (normal 3:1), the iron content, the presence of inclusions (such as LD bodies in kala azar) and storage products (lipidoses).

➢ Bence-Jones proteins are free Ig light chains seen in the urine of patients with multiple myeloma.

➢ Hb studies are indicated in suspected hemolytic disorders; they include Hb electrophoresis, meth-Hb assay and G-6 PD assays.

15.4 Anemias

We have earlier provided a qualitative definition of anemia in Chapter 15.2. However, clinical evaluation requires interpretation of quantitative laboratory values. In this context, anemia has been defined as a value of hemoglobin below two standard deviations of the normal value for that age-group and sex. The WHO has empirically defined anemia as a value of hemoglobin: less than 13 g/dL in a man, less than 12 g/dL in a non-pregnant woman, or less than 11 g/dL in a pregnant woman. When hematocrit is used to identify anemia, it has been suggested that a value less than 37 per cent in women and less than 39 per cent in men be used as cutpoints for defining anemia.

Iron Deficiency Anemia

Iron deficiency anemia is one of the mos widely prevalent nutritional disorders in India.

Iron metabolism (Fig 15.6)

Iron is the most abundant metal in the body an the body stores of iron varies from 2 g in wome to 6 g in men. The bulk of the iron is present i hemoglobin, myoglobin and enzymes such a catalase and cytochromes. The chief functions o the mineral are participation in cellula respiration, oxygen transport and ce proliferation.

Dietary iron exists in two forms: *hem* (available in animal food) and *non-heme* iro (plant food). The absorption from each sourc

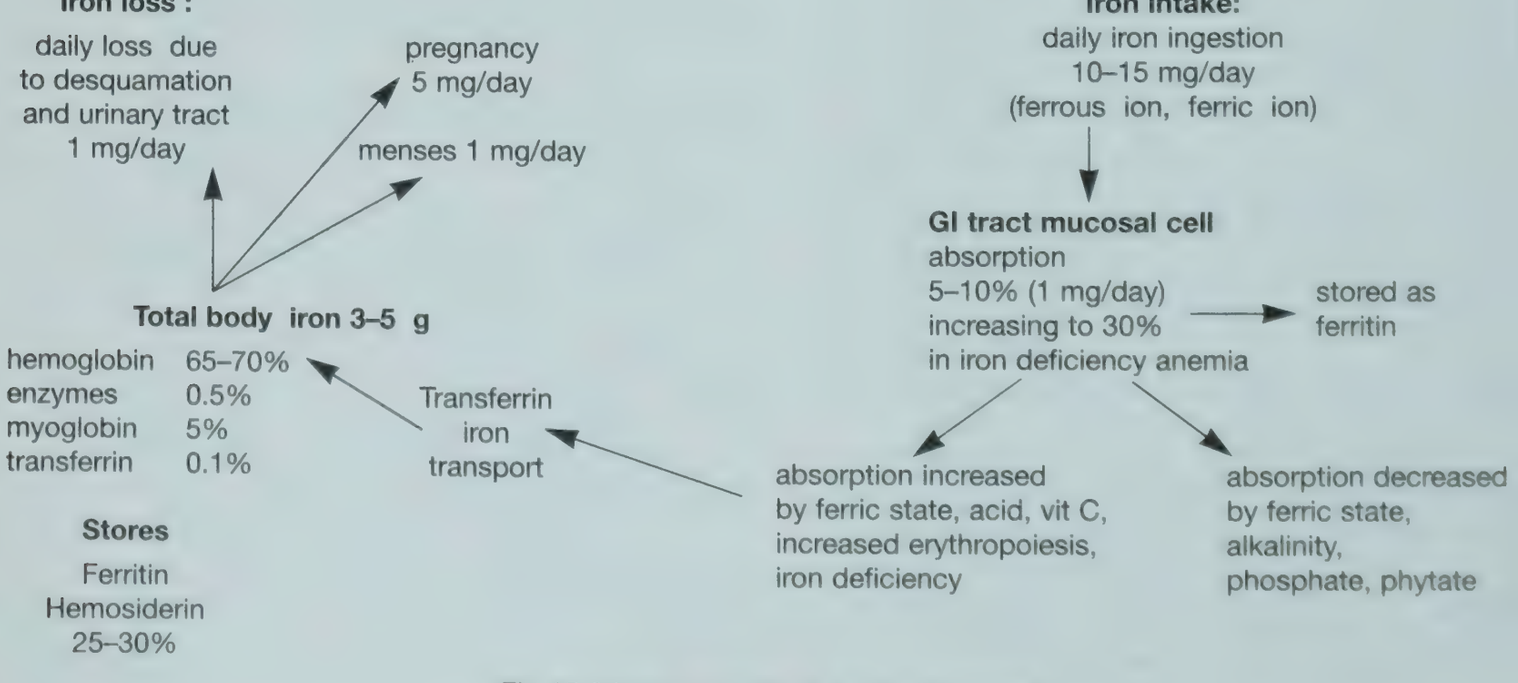


Fig 15.6 Iron metabolism and iron balance

varies. After ingestion, heme, complexed with apoprotein is broken down in the stomach to release free heme. This is absorbed intact in the proximal part of the gut. The absorption of non-heme iron is less clearly understood. Whatever be the source of iron, the absorbed mineral enters a common pool in the mucosal cell. A fraction of iron from the mucosal cell is taken up by transferrin. The remaining iron is deposited as ferritin. The high cell turnover of the gastrointestinal mucosal cells lead to exfoliation and loss of mucosal iron. Daily losses range between 1–1.5 mg of iron. Absorption of iron is regulated at the level of the mucosal cell. If body stores are in excess, mucosal absorption of iron is reduced. This is known as '*mucosal block*'.

Ferritin (a storage form of iron) is a protein-iron complex which is not only found in the mucosal cell but also in the hepatocytes, the mononuclear phagocytie cells of the marrow, spleen and liver. A small quantity of ferritin circulates in plasma as plasma ferritin. Estimation of plasma ferritin gives an idea about the iron stores in the body. Iron is also stored as *hemosiderin* granules. In times of need, iron stored as ferritin and hemosiderin is mobilised for heme synthesis. *Transferrin* is a glycoprotein (synthesised in the liver) which is responsible for the transport of iron. It has two iron-binding sites. In a normal healthy person, the binding sites of transferrin are one-third saturated with iron (33 per cent). Thus, though total iron binding capacity (TIBC) is 300–350 µg/dl, the normal serum iron level is only 100–120 µg/dl. Transferrin transports iron to the liver for storage and to the erythroid precursors for heme synthesis. The erythroid precursors are endowed with receptors which have an increased affinity for transferrin. The iron from the transferrin is taken up by the cell and the transport protein is released. The iron obtained from dying RBCs is taken up by the macrophages. Seventy five per cent of this iron is taken up by transferrin and transferred to the erythroid precursors. Thus, iron is recycled within the body. In diseased conditions, the transfer of iron from the macrophages to the erythroid cells is inhibited leading to anemia in spite of adequate iron stores. The causes of iron deficiency are shown in Table 15.9.

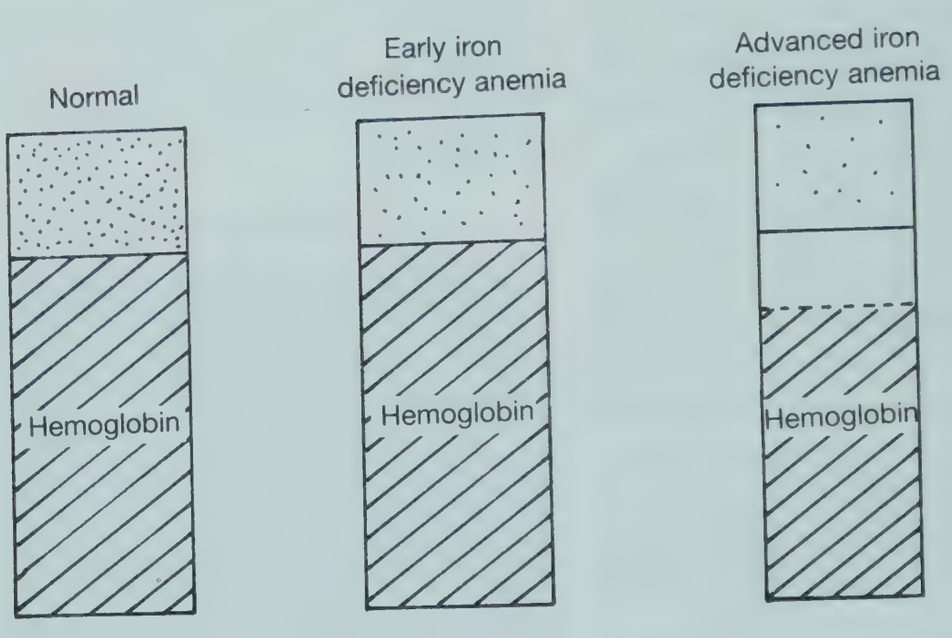
Table 15.9 Causes of iron deficiency anemia

1. Deficiency in the diet
2. Decreased absorption
   - gastrectomy
   - achlorhydria
   - malabsorption
   - ingestion of dirt
3. Increased loss
   - GI bleed
   - hookworm infestation
   - menstrual bleeding
   - pregnancy, lactation
   - paroxysmal nocturnal hemoglobinuria
   - phlebotomies
   - idiopathic pulmonary hemosiderosis
4. Increased requirement
   - small-for-gestation babies
   - preterm babies

Pathophysiology The earliest feature of iron deficiency anemia is depletion of ferritin and hemosiderin from the marrow. Plasma ferritin decreases and transferrin levels increase. Serum iron falls and iron binding capacity rises. Free erythrocyte protoporphyrin (FEP) levels increase: these are the precursors of heme synthesis. Normocytic normochromic anemia ensues initially. With persistent iron deficiency microcytes appear (increasing anisocytosis or RDW). Subsequently the RBCs become microcytic and hypochromic (Fig 15.7).

Clinical features Pallor is the predominant presenting feature. Abnormalities of the epithelium causes glossitis, papillary atrophy, dysphagia and *koilonychia.*[1] Pica is an unusual but specific manifestation of iron deficiency anemia. Dysphagia due to a cricoid

[1] Koilonychia means 'spoon-like convex nails'.



marrow iron	N	absent	absent
serum ferritin	N (20–250 μg/dl)	low	low (<12 μg/dl)
serum iron	N (65–175 μg/dl)	N	low (<30 μg/dl)
serum iron binding capacity	N (300–360 μg/dl)	N	↑ (400 μg/dl)
transferrin saturation	N (25–50%)	N	↓ <16%
erythrocyte free protoporphyrin	N (27–61 μg/dl)	N	↑ (>180 μg/dl)
MCV (fl)	N (80–100)		↓ (<80)

Fig 15.7 Sequence of changes in iron metabolism in iron deficiency anemia

esophageal web (*Patterson-Kelly* or *Plummer-Vinson syndrome*) is rarely associated with iron deficiency anemia.

Treatment The cause of iron deficiency anemia should be identified and treated (Table 15.10). 200 mg of elemental iron three times a day taken prior to meals is sufficient to treat these conditions. Rarely, in cases of intolerance to oral iron or in malabsorption syndromes, parenteral iron may be required. Iron-dextran may be given intravenously (500 mg diluted in 100 ml saline, given over 2 hours after an initial test dose) or by the intramuscular route (100 mg per injection, given using a Z-tract technique after an initial test dose). An outline of the management of iron deficiency anemia is shown in Fig 15.8.

MEGALOBLASTIC ANEMIA

The megaloblastic anemias are a group of disorders which result from impaired DNA synthesis. They have a characteristic morphology of the erythrocyte and the precursor cells in the marrow in common.

Pathophysiology In megaloblastic anemia the red blood cells are larger (*megaloblastoid*) than normal with a 'macroovalocyte'[1] pattern (the mean corpuscular volume is > 100 fl). They lack the central pallor seen in normal red blood cells and the MCHC is normal. The neutrophils are also larger than normal and have

[1] Macroovalocyte is a large oval cell

Table 15.10 Response to iron therapy in iron deficiency anemia

Time after iron administration	*Response*
12–24 hours	replacement of intracellular iron enzymes, subjective improvement, decreased irritability, increased appetite
36–48 hours	erythroid hyperplasia
48–72 hours	reticulocytosis begins, peaks at 5–7 days
4–30 days	increase in Hb level
1–3 months	repletion of stores

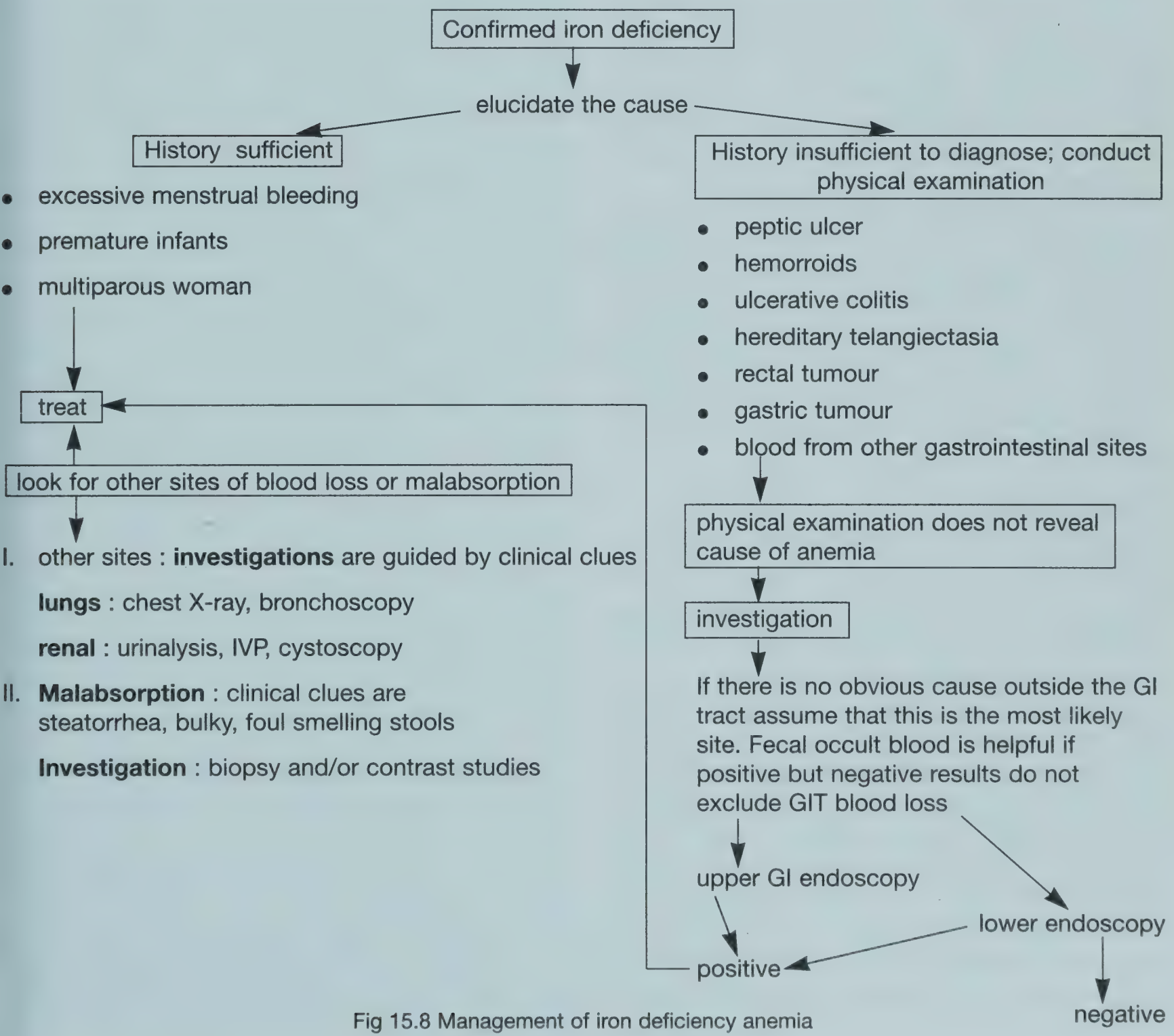


Fig 15.8 Management of iron deficiency anemia

a hypersegmented nucleus (which has more than five lobes). The platelets are reduced in number.

Within the marrow, the megaloblastoid appearance is obvious in all stages of development of the individual cell lines. As has been discussed earlier, the normoblast has a nucleus with a fine chromatin network. As the cell matures, the chromatin condenses, becomes pyknotic and is extruded. The basophilic cytoplasm hemoglobinises and the entire cell becomes much smaller.

In megaloblastic anemia, normal DNA metabolism fails to occur. There is a delay in nuclear maturation. RNA metabolism proceeds normally and therefore, the cytoplasmic maturation is normal. An asynchronism between DNA and cytoplasmic maturation (*nuclear-cytoplasmic dissociation*) results in the typical megaloblastic picture of all cell lines.

Anemia occurs due to ineffective erythropoiesis and an increased destruction of the abnormal red blood cells. This stimulates the bone marrow which becomes hypercellular. Causes of megaloblastic hematopoiesis include folate and B_{12} deficiency, acute leukemia, myelodysplastic syndromes and chemotherapy (Table 15.11)

Clinical features

When faced with a subject with macrocytic anemia, the physician must obtain a careful history to detect the possible underlying cause. A history of chronic alcohol intake, smoking, chronic liver disease is carefully sought.

The anemia is usually of insidious onset. On physical examination glossitis often coexists. Heart failure, hepatosplenomegaly and purpura are some of the rare manifestations of the severe disease. Megaloblastic anemia due to B_{12} deficiency can be differentiated from that of folate deficiency by the presence of *subacute combined degeneration* of the dorsal and lateral columns of the spinal cord in the former. Loss of fine touch, vibration sensation, paresthesiae of the 'glove and stocking'

Table 15.11 Causes of megaloblastic anemia

A. **Causes of folate deficiency**

1. Decreased intake
   - inadequate diet-alcoholism, infancy
   - impaired absorption-malabsorption states (tropical sprue), intrinsic intestinal disease, anticonvulsants, oral contraceptives
2. Increased loss
   - hemodialysis
3. Increased requirement
   - pregnancy
   - Infancy
   - disseminated cancer
   - markedly increased hematopoiesis
4. Impaired utilisation
   - folic acid antagonists (methotrexate)

B. **Causes of vitamin B_{12} deficiency**

1. Decreased intake
   - inadequate diet
   - impaired absorption
     - intrinsic factor deficiency
       - pernicious anemia
       - gastrectomy
       - malabsorption states
     - diffuse intestinal disease
       - lymphoma, systemic sclerosis
       - ileal resection, ileitis
     - competitive parasitic uptake
       - fish tapeworm infestation
2. Increased requirement
   - bacterial overgrowth in blind loops and diverticula of bowel
   - pregnancy
   - hyperthyroidism
   - disseminated cancer

C. **Metabolic disorders**

Unresponsive to vitamin B_{12} and folic acid therapy

- metabolic inhibitors e.g., mercaptopurine, fluorouracil
- unexplained disorders – pyridoxine and thiamine-responsive megaloblastic anemia
- acute erythroleukemia (M_6)

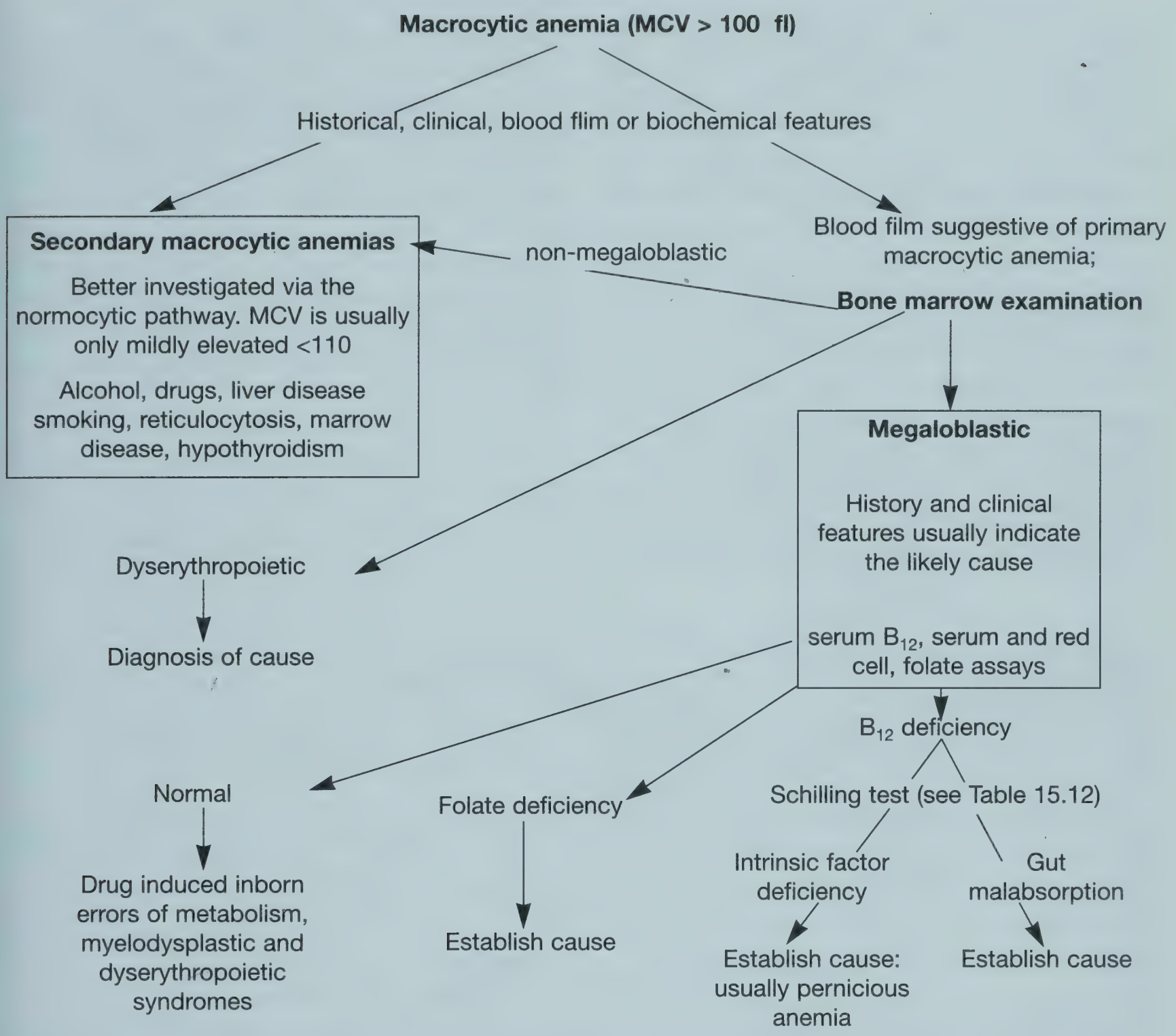


Fig 15.9 Investigation of macrocytic anemia

distribution are the early features, while spasticity with ataxia develop later in the course of the disease.

Investigations Careful examination of the peripheral smear may yield useful clues to the etiology of macrocytic anemia.

Oval macrocytes and hypersegmented polymorphonuclear cells are pointers towards megaloblastosis. Round, thin macrocytes and target cells suggest liver disease; alcoholism is the likely culprit if stomatocytes are present. Polychromasia, suggesting an elevated reticulocyte count, is a pointer towards an underlying hemolytic anemia. A bone marrow biopsy is diagnostic in megaloblastic anemia with evidence of nuclear cytoplasmic dissociation seen along all cell lines.

Serum vitamin B_{12}, serum and red cell folate levels can be estimated if facilities are available to distinguish folate deficiency from vitamin B_{12} deficiency. The diagnostic approach is depicted in Fig 15.9.

Normal folate and B_{12} metabolism (Fig 15.10)

Folic acid (Pteroyl glutamic acid) Folic acid is a vitamin found in yeast, dark green leafy vegetables and in fruits. Pteroyl glutamate is broken down into monoglutamates and absorbed in the proximal third of the intestine. After absorption it is reduced by the enzyme tetrahydrofolate reductase. The 'reduced' folate can now accept one-carbon fragments from compounds such as formiminoglutamate and serine. The carbon units are transferred to form biologically active end products. Important metabolic processes where folate is involved include the synthesis of purines, deoxythymidylate monophosphate and the formation of methionine from homocysteine. All these metabolites are necessary for normal nucleic acid metabolism.

Vitamin B_{12} Vitamin B_{12} consists of a *corrin ring* containing a cobalt atom. It is also therefore known as cobalamine. Foods rich in vitamin B_{12} include sources like liver, eggs, kidney and milk.

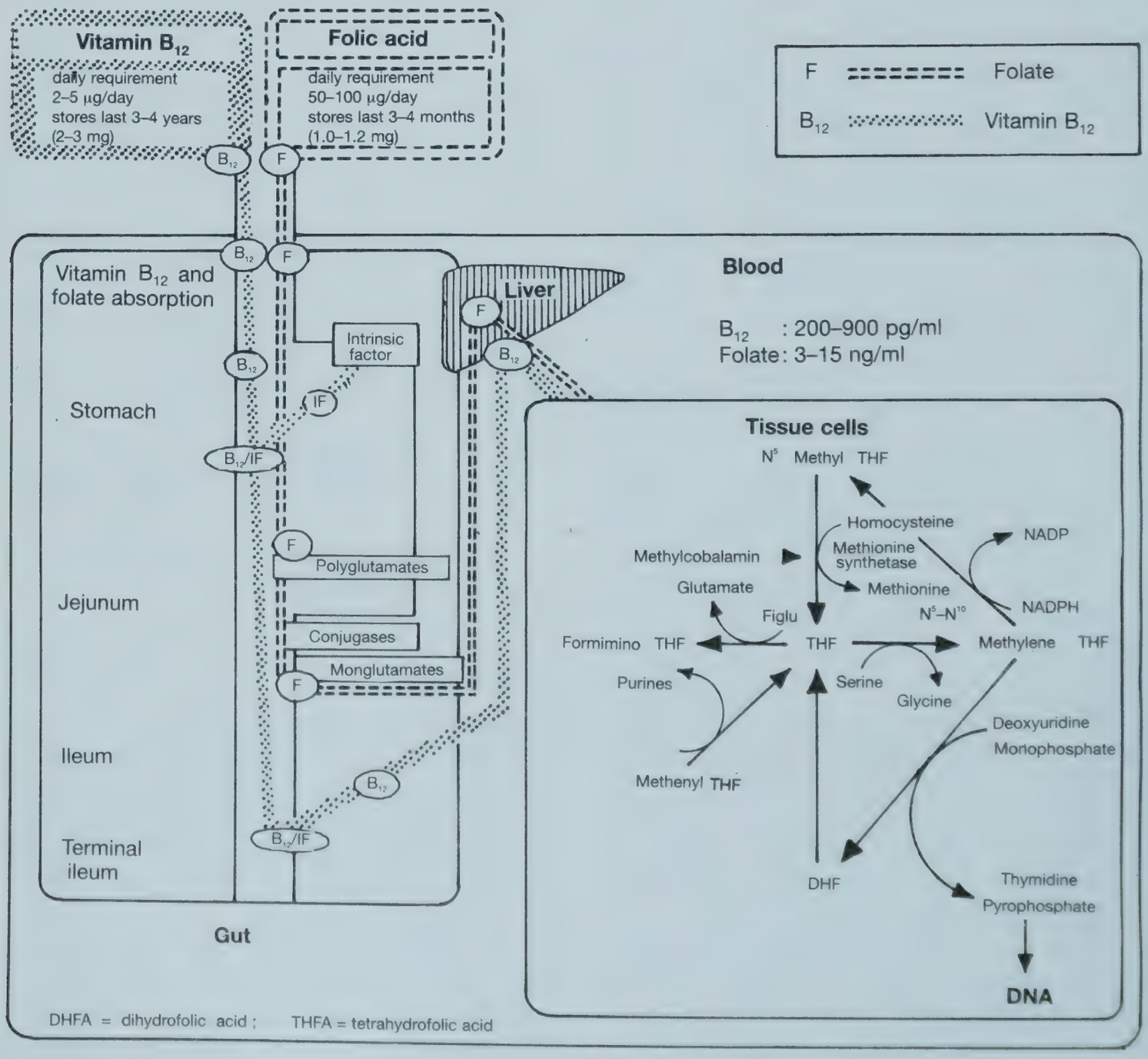


Fig 15.10 Folate and vitamin B_{12} metabolism

In the stomach, peptic digestion of food releases the B_{12} which binds to certain binding proteins known as '*R-binder proteins*'. Pancreatic proteases break down this complex thereby releasing vitamin B_{12}. The latter combines with the intrinsic factor which is secreted by the gastric fundus. The *B_{12}-IF complex* reaches the ileal mucosal cell where B_{12} alone enters the cell leaving behind the intrinsic factor. The B_{12} is 'picked up' by *transcobalamine II*, a transport protein and transported to the marrow, liver and other organs.

The daily requirement of vitamin B_{12} is 1 μg. Since the body stores are large and most of the B_{12} is conserved during the enterohepatic circulation of the vitamin, deficiency states arise due to chronic malabsorption rather than from poor intake. On the other hand, body stores of folic acid are limited and a diet deficient in folate will lead to megaloblastic anemia over a period of a few months. The daily requirement of folate in the adult is approximately 50 μg.

Biochemistry Vitamin B_{12} participates in two metabolic processes:

1. conversion of homocysteine to methionine. The latter reaction links B_{12} to folate metabolism. Thymidylate is essential for DNA synthesis. Formation of thymidylate requires the transfer of a methylene group from N_5–N_{10} methylene tetrahydrofolate. The immediate precursor of the latter is tetrahydrofolate. Tetrahydrofolate is produced by the conversion of homocysteine to methionine, a reaction which needs vitamin B_{12} as a coenzyme. Hence deficiency of vitamin B_{12} causes folate deficiency which, in turn prevents nucleic acid synthesis and therefore nuclear maturation (Fig 15.9)
2. B_{12} also serves as a coenzyme in the conversion of methyl malonyl Co A to succinyl Co A. B_{12} deficiency increases methyl malonyl Co A levels, a factor which predisposes to myelin breakdown. The neurologic manifestations of B_{12} deficiency have been attributed to this metabolic abnormality.

Pernicious Anemia

It is an inherited, autoimmune disorder characterised by gastric mucosal atrophy resulting in the failure of secretion of intrinsic factor. The latter causes the development of megaloblastic anemia secondary to vitamin B_{12} malabsorption. Achlorhydria and failure to secrete intrinsic factor are due to autoimmune antibodies targeted against parietal cells in 80 per cent of patients, and against intrinsic

Table 15.12 Schilling test

Step 1	Oral administration of tracer dose of radioactive vitamin B_{12}
Step 2	Saturation of binding sites by parenteral injection of 1 mg unlabelled vitamin B_{12}
Step 3	Collection of urine for 24 hours on two successive days for radioactivity measurements
Step 4	Normally greater than 9 per cent of administered radioactive dose is excreted in urine in the first 24 hours.
Step 5	If urinary excretion is <9%, repeat test with radiolabelled vitamin B_{12}–intrinsic factor complex. If on repeat testing urinary excretion of radiolabelled vitamin B_{12} is >9%, intrinsic factor deficiency is the likely cause of megaloblastic anemia
Step 6	If on repeat testing with B_{12}–IFcomplex urinary excretion is <9%, the test is repeated after a course of antibiotics. Normalisation after antibiotic therapy indicates 'bacterial overgrowth' syndrome as the cause of vitamin B_{12} malabsorption.

factor in 50 per cent of patients. These antibodies are easily detected in the serum.

Thyroid antibodies, lymphocytotoxins and rheumatoid factors can also be identified. These antibodies account for the high incidence of endocrinologic disorders associated with pernicious anemia. Patients with pernicious anemia have an increased risk of developing gastric polyps and gastric carcinoma. They also suffer from subacute combined degeneration of the spinal cord, a clinical feature associated with B_{12} deficiency.

Investigation (Table 15.12) Low serum B_{12} levels and an abnormal Schilling test corrected by addition of intrinsic factor is confirmatory of the disease.

Teatment of megaloblastic anemia In pernicious anemia, hydroxycobalamin is administered parenterally as dose 100 µg/day for seven days followed by 100 µg weekly for five weeks in order to replenish body stores. 100 µg of vitamin B_{12} is administered monthly thereafter for life. Folate deficiency is treated with 1 mg/day orally; a higher dose (5 mg/day) may be needed in malabsorption syndromes.

Hemolytic Anemias

These are hereditary or acquired disorders of the red cell membrane or metabolism which are characterised by increased destruction of erythrocytes. A classification is displayed in Table 15.2.

Congenital spherocytic anemia

Congenital spherocytic anemia (CSR) is an inherited disorder of the red cell membrane wherein the biconcave, deformable erythrocyte is transformed into a rigid spherocyte which is susceptible to intrasplenic sequestration and hemolysis.

Genetics It is inherited as an autosomal dominant disorder.

Pathophysiology The structural protein of the red cell membrane is known as *spectrin*. It comprises of a pair of polypeptide chains entwined and attached to the cytoplasm by another protein *ankyrin*. Abnormality of spectrin renders the cell membrane susceptible to damage. Loss of cellular membrane results in reduction in cell surface–volume ratio which converts the biconcave disc into a sphere to assume the smallest possible diameter for a given volume. The rigid sphere is unable to negotiate the narrow splenic cords leading to increased membrane damage which ultimately causes cell death by osmotic lysis and destruction by splenic macrophages.

Clinical features Severe pallor, icterus and splenomegaly may be present at birth, often necessitating an exchange transfusion. Chronic hemolysis is occasionally complicated by a transient aplastic crisis similar to that seen in sickle cell disease. An acute hemolytic crisis may be precipitated by intercurrent infections. It is characterised by severe pallor, jaundice, abdominal pain, vomiting and features of shock.

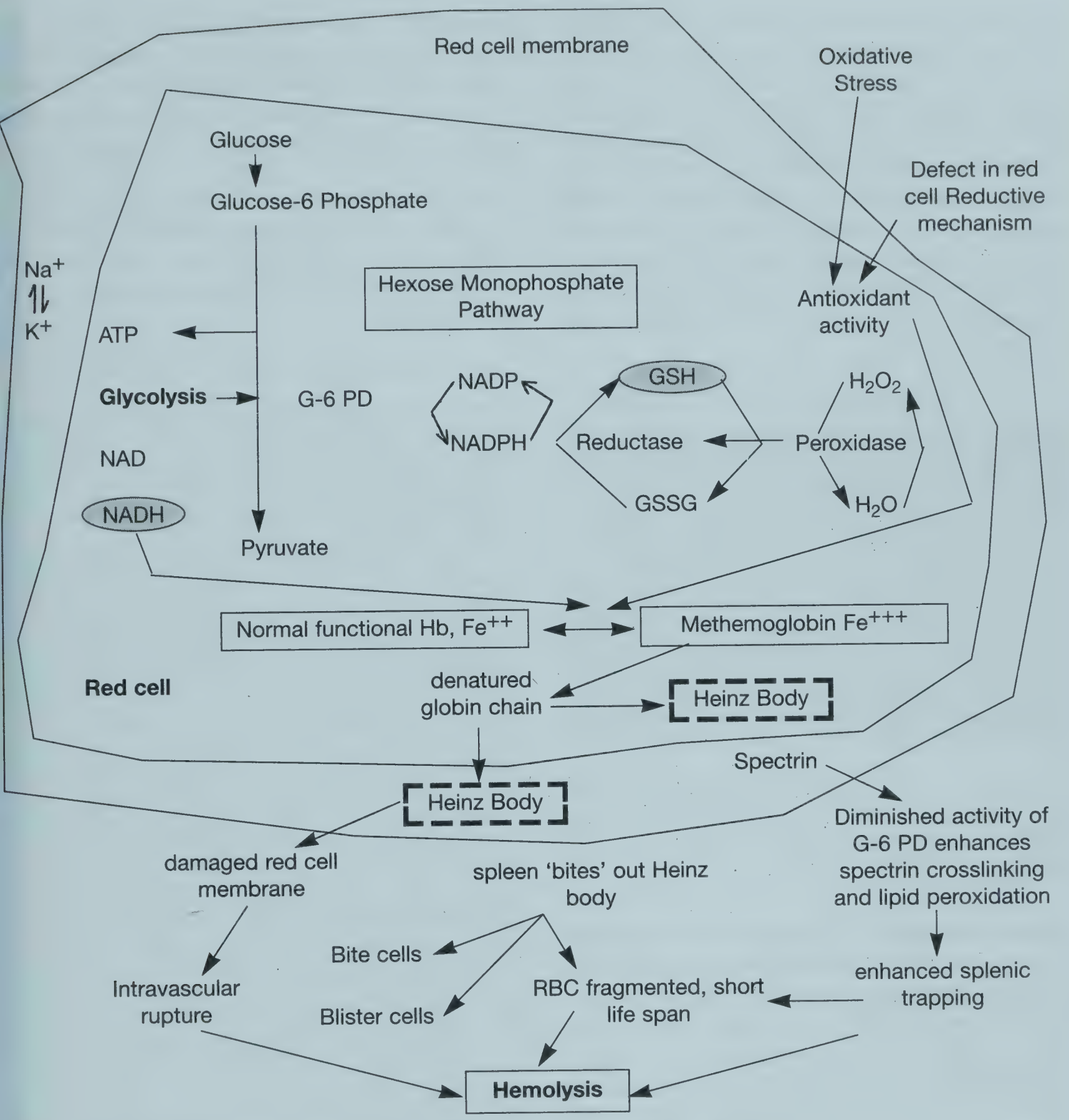
Investigations The peripheral blood film shows spherocytes and polychromatophilia. The MCV is normal and MCHC is elevated to 37–39 g/dl. The osmotic fragility is increased. Since spherocytes are also a feature of AIHA, a Coomb's test is performed to rule out the latter diagnosis.

Management The hemolytic process of congenital spherocytic anemia is relieved by splenectomy. Though the spherocytes persist, the risk of intrasplenic hemolysis is eliminated.

Glucose-6 Phosphate dehydrogenase deficiency

Glucose-6 phosphate dehydrogenase (G-6 PD) is often referred to as the 'housekeeping enzyme' since it helps in eliminating the oxidants which are potentially injurious to the cell.

Pathophysiology G-6 PD is necessary for the second step of the hexose monophosphate shunt



NAD = nicotinamide adenine dinucleotide
NADH = reduced form of NAD
NADP = nicotinamide adenine dinucleotide phosphate
NADPH = reduced form of NADP
GSH = reduced form of glutathione
GSSG = oxidised form of gultathione
ATP = adenosine triphosphate
Na^+ = sodium ion
K^+ = potassium ion
Fe^{++} = ferrous ion
Fe^{+++} = ferric ion
Hb = hemoglobin
spectrin = RBC membrane protein

Bite cells are pitted cells with the Heinz bodies removed by splenic phagocytes; blister cells are cells with submembranous hemoglobin free areas

Fig 15.11 Mechanisms of hemolysis in G-6 PD deficiency

pathway of carbohydrate metabolism where the H^+ ion released is taken up by NADP to form NADPH. The H^+ ion is transferred to the sulphydryl group of glutathione, a compound universally produced by all cells. When the cell is exposed to oxidant stress, the H^+ ion from GSSH neutralises the oxygen radical, thereby preventing cell injury and death. In the absence of G-6 PD, the toxic effects of oxidant drugs result in cell lysis (Fig 15.11). The clinical illness depends on the level of G-6 PD activity in the cell (Table 15.13).

Table 15.13 Clinical severity of G-6 PD deficiency

Class	*Level of enzyme activity*	*Clinical feature*
I	< 10%	continuous ongoing hemolysis
II	> 10%	acute episodes of hemolysis
III	> 10–60%	episodes of hemolysis on exposure to oxidant drugs
IV	> 60%	normal

Genetics The enzyme deficiency is inherited as an X-linked recessive trait. The defect is more common in the Parsee and Lohana communities in India.

Clinical features The disease can manifest in the immediate newborn period as neonatal hyperbilirubinemia and kernicterus. It can occur either spontaneously or following the ingestion of the oxidant drugs. In older patients, features characteristic of acute hemolysis, like pallor, jaundice, splenomegaly, abdominal pain and hemoglobinuria can occur within 48–96 hours after intake of drugs. The hemolysis is self-limiting and recovery usually occurs 3–4 days after the onset of symptoms. Occasionally the hemolytic reaction can also be fatal.

Investigations In the unstained peripheral blood smear or in a blood smear stained with supravital dyes *Heinz bodies*[1] can be demonstrated. *Bite cells*[2] are also characteristic. The hemoglobin level drops down to as low as 2–10 g/100 ml of blood. Demonstration of the enzyme deficiency in the RBC is diagnostic.

Treatment Patients suffering from this disorder should avoid drugs which can induce hemolysis (Table 15.14). Transfusions help tide over the crisis of severe anemia. Splenectomy is, however, not beneficial.

Table 15.14 Drugs to be avoided in G-6 PD deficiency

Antimalarials
- primaquine
- chloroquine

Sulphonamides and sulphones
- sulphanilamide
- sulphapyridine
- sulphadimidine
- sulphacetamide
- sulphafurazone
- salicylazosulphapyridine
- dapsone
- cotrimoxazole

Other antibacterial compounds
- nitrofurans
  - nitrofurantoin
  - furazolidone
  - nitrofurazone
- nalidixic acid
- chloramphenicol
- p-aminosalicylic acid

Analgesics
- acetylsalicylic acid (Aspirin)
- acetophenetidin (phenacetin)

[*Safe alternative :*
- Paracetamol]

Antihelmintics
- Niridazole

Miscellaneous
- Vitamin K analogues
- Naphthalene
- Probenecid
- Dimercaprol

[1] Heinz bodies are denatured hemoglobin.

[2] Bite cells refer to the removal of denatured hemoglobin within the spleen. (Splenic pH causes the RBC to assume the characteristic shape.)

Advantages of G-6 PD deficiency G-6 PD deficiency confers protection against plasmodium falciparum malaria. It has been observed that the distribution of the G-6 PD deficiency trait is more where malaria is common. There is enhanced protection against malaria, particularly in heterozygote females. The reason for this protective effect is unclear. It has been postulated that poor parasite adaptation may result from the exposure to two different cell lines, one deficient in G-6 PD and the other rich in G-6 PD.

Acquired Hemolytic Disorders

Paroxysmal nocturnal hemoglobinuria

Definition This is an uncommon hematological disorder, the etiology of which is not fully known. It is characterised by chronic intravascular hemolysis which worsens in the night. Hemoglobinuria is not a very obvious feature but chronic destruction of the red blood cells results in iron deficiency anemia. Infections occur with increased frequency secondary to abnormal leukocyte function. Thrombosis in the portal and cerebral veins result from platelet abnormalities and are a common cause of death in this disease.

Pathophysiology A disorder of the multipotent stem cell results in an abnormal clone of cells with increased susceptibility to spontaneous complement-mediated lysis. The increased sensitivity to complement is due to deficiency of

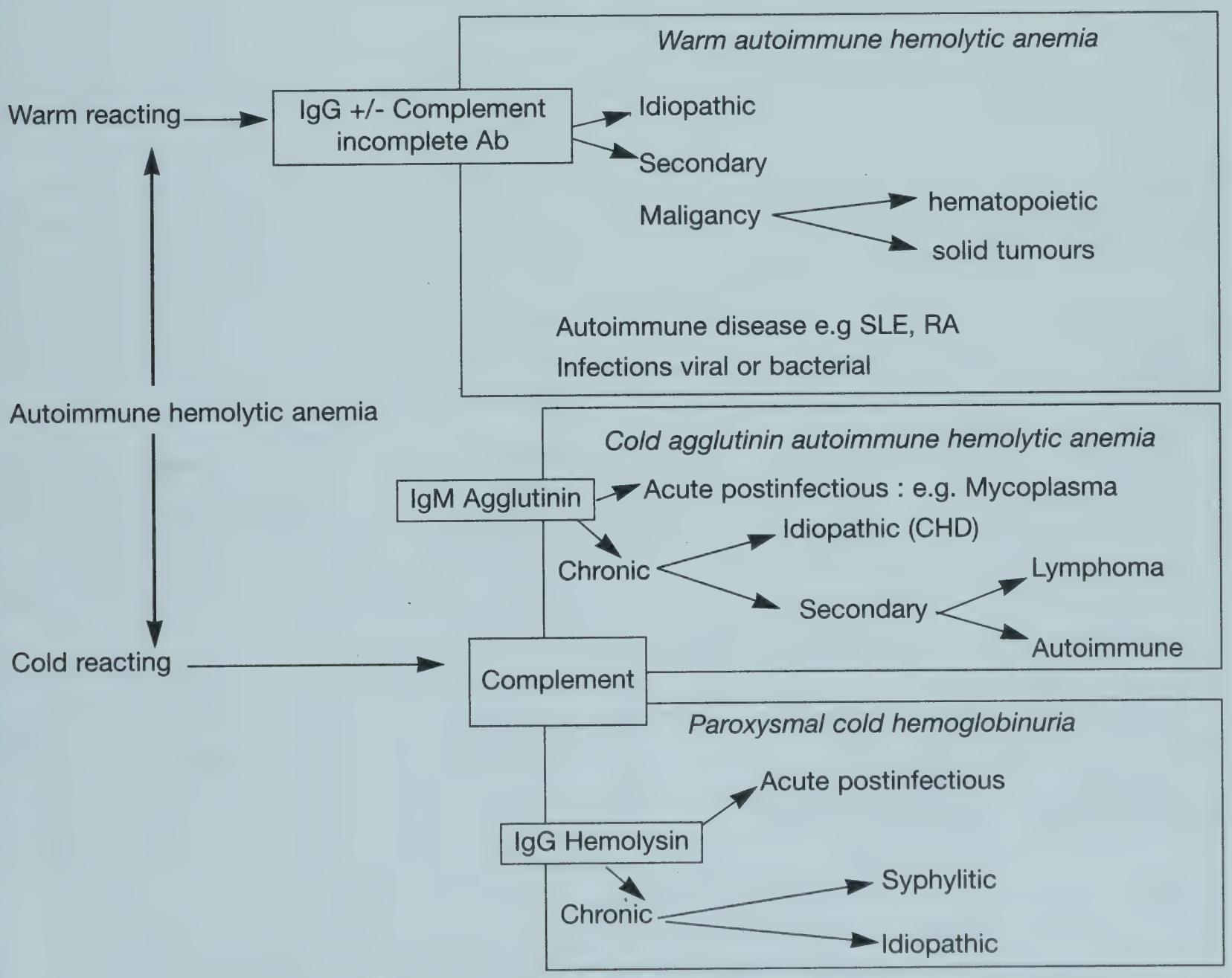


Fig 15.12 Classification of autoimmune hemolytic anemia; Ab = antibody

cell membrane glycoproteins called *decay accelerating factor* (DAF) and membrane inhibitor of reactive lysis (MIRL). The defect involves the red and white blood cells and also platelets accounting for the predisposition to intravascular thrombosis, infections and hemolysis.

Investigations Cells from the patients with PNH when incubated in acidified serum lyse more readily than normal cells (*Ham's test*). The affected cells also lyse in sucrose solution. A bone marrow aspirate reveals hypoplasia, a feature which exists in spite of hemolysis. Leucocyte alkaline phosphatase (LAP) levels are low.

Treatment is symptomatic. Severe anemia is treated with blood transfusion. Leukocyte-poor blood is preferred in order to avoid complement-induced hemolysis. Anticoagulants are useful in the management of thrombotic episodes.

Prognosis Spontaneous recovery occurs when the abnormal clone disappears from the marrow. This, however, occurs very rarely.

Immune hemolytic anemia

Immune hemolytic anemia is an acquired disease resulting from autoantibodies directed against the patient's own RBCs.

Autoantibodies which cause hemolysis at 37°C are characteristic of *warm autoimmune hemolytic anemia* (AIHA), whereas antibodies which are reactive at 4°C are the peculiarity of cold AIHA, also known as *cold agglutinin disease* (Fig 15.12). A classification of AIHA is depicted in Table 15.15.

Warm AIHA is the most common variety of autoimmune hemolytic anemias.

It occurs with equal frequency in all ages. The disorder is more common in women.

Pathophysiology The autoantibodies which coat the RBCs and cause hemolysis are of the IgG variety. Mononuclear phagocytes possessing Fc receptors for the IgG immunoglobulin engulf the opsonised RBC. Sometimes the red cell membrane undergoes only partial damage resulting in swelling of the damaged cell giving rise to a spherocyte. Such cells are at increased risk of premature destruction particularly in the spleen.

Table 15.15 Classification of AIHA

1. Warm AIHA
   a. Primary or idiopathic AIHA
   b. Secondary warm AIHA
      collagen vascular disease
      lymphoproliferative disorder
2. Cold AIHA (CAD)
   a. Primary cold AIHA
   b. Secondary cold AIHA
      mycoplasma infection
      infectious mononucleosis
      lymphoproliferative disorders
   c. paroxysmal cold hemoglobinuria
3. Drug-induced AIHA

Clinical features Progressive anemia in patients with underlying systemic illnesses like systemic lupus erythematosus or lymphoma often bring the disease to notice. Jaundice, fever and hemoglobinuria are less common presenting features. Splenomegaly occurs in 50 per cent and hepatomegaly in a third of the patients.

Investigations The hemoglobin concentration falls to 7 g/dl. The peripheral smear shows spherocytes, autoagglutination and polychromasia. The reticulocyte count is elevated. A positive direct Coomb's test[1] is the hallmark of the disease.

Treatment Reduction of hemolysis is achieved in 80 per cent of patients by the administration of steroids. As the anemia improves the steroids are tapered. Hemolytic anemia which is unresponsive to steroids or which renders the patient steroid-dependent is controlled by performing a splenectomy.

[1] Coomb's test consists of incubating the patient's red cells with antihuman IgG (goat or rabbit origin). A positive reaction is determined by the presence of agglutination.

old agglutinin disease

his disease accounts for 15 per cent of AIHA nd is seen more frequently in the middle aged nd in the elderly patients. Anemia and emoglobinuria are precipitated on exposure to old. The condition is commonly associated with n underlying lymphoproliferative disorder, pstein-Barr infection or mycoplasma neumonia.

athophysiology In the extremities where e temperature is low, IgM autoantibodies bind the patient's RBCs. These have the capacity fix complement. Hepatic macrophages nagocytose the C3b-coated RBCs (unlike arm AIHA where the splenic macrophages are ne prime effector cells in destroying the psonised RBCs).

vestigations Autoagglutination, spherocytes nd polychromatophilia are characteristic atures in the peripheral blood film. A positive rect Coomb's test with complement nsitisation is diagnostic. Cold-reactive IgM ntibodies at titres above 1000 can be emonstrated at 4°C by immunoassay.

reatment Exposure to cold is avoided. teroids and splenectomy are ineffective. Severe nemia is corrected by transfusion.

aroxysmal cold hemoglobinuria

his is an autoimmune hemolytic disorder aused by an IgG autoantibody which is reactive gainst the red cell P antigen. It binds to the BCs on exposure to cold. On warming to 30°C omplement activation occurs which in turn nduces red cell lysis.

It is also a self-limiting disorder usually llowing an acute viral illness. It is characterised y fever, chills, abdominal pain and hemo-lobinuria. The disease is diagnosed by the *Donath-Landsteiner test*. The patient's serum ith cells is incubated at 4°C and then warmed o induce complement activation. Presence of ne autoantibody results in hemolysis.

Drug-induced AIHA

About 10 per cent of AIHAs are due to drugs. Methyldopa, penicillin and quinidine are usually involved. These drugs probably cause hemolysis by inducing an immune complex type mechanism. Anemia develops gradually after ingestion of the offending drug. As in other AIHA, a positive direct Coomb's test confirms the presence of this disease. Therapy involves discontinuation of the offending drug.

HEMOGLOBINOPATHIES

Thalassemias

The thalassemias[1] are a heterogeneous group of hereditary disorders of hemoglobin synthesis characterised by and are decreased globin synthesis.

Pathophysiology Thalassemia is inherited as an autosomal codominant condition. There are two types of globin chains: alpha (α) and beta (β). Hence, diseases affecting each type helps classify the thalassemias into alpha-thalassemia and beta-thalassemia. The basic defect in beta-thalassemia is that the β-globin chain is either absent (β_0) or deficient (β^+). In alpha-thalassemia the α-globin production is reduced. Deficient synthesis of α- or β-globin chains with continued normal synthesis of unaffected chains result in the following:

Reduced β-globin synthesis leads to insufficient hemoglobin A resulting in hypochromic red blood cells. The excess α chains form insoluble aggregates which precipitate within the RBC. The latter damages the red cell membrane rendering it susceptible to phagocytosis by the macrophages. Presence of these inclusions within the immature erythroblasts leads to their premature destruction within the bone marrow. Thus, the anemia in thalassemia results from decreased synthesis of normal hemoglobin, ineffective erythropoiesis and hemolysis. Anemia is a stimulus for erythro-

[1] Thalassa means 'the great sea' in Greek

poiesis. Therefore, the bone marrow expands impinging on the normal bone. This causes distortion of the cranial, facial and long bones. Hematopoiesis is not restricted to the bone marrow. Extramedullary hematopoiesis occurs in the liver, spleen and lymph nodes causing the enlargement of these organs. Regular blood transfusions, the mainstay of therapy in this disorder, cause an increased turnover of iron. Deposition of excess iron in the liver, the endocrine organs, the heart and skin result in secondary damage and failure of the vital organ functions.

Alpha-thalassemia

There are four genes responsible for the production of the two alpha chains. Thus, four types of α-thalassemia syndromes result depending on the number of gene deletions as shown in Table 15.16.

Beta-thalassemia

They are classified according to the severity of the anemia. The heterozygous states include *thal minima* and *thal minor* whereas the homozygous states include *thal intermedia* and *thal major*, that is, when an affected gene is inherited from both the parents the homozygous state results in a severe form of the disease. When the affected gene is inherited from only one parent, a milder condition occurs (Table 15.17).

Clinical features Thalassemia major becomes symptomatic in the latter half of the first year with severe pallor and jaundice as the presenting features. The child fails to thrive. Growth is stunted due to chronic anemia and decreased somatomedin production. Regular transfusions are necessary to sustain life. Expansion of the bone marrow results in frontal bossing malocclusion of the mandible, maxillary

Table 15.16 Alpha-thalassemia syndromes

Syndrome	*Gene deletions*	*No. of normal genes*	*Anemia/ microcytosis*	*Hemoglobin at birth*	*Electrophoresis as an adult*	*Comments*
α-thalassemia trait-2 (silent carrier)	1	3	none/none	1–2% BARTS	normal	clinically and hematologically normal
α-thalassemia trait-1 (heterozygous state)	2	2	mild/present	5–10% BARTS	normal	mild anisocytosis, unresponsive to therapy
hemoglobin H disease (α-thal-2+ α-thal -1	3	1	moderate/ marked	20–40% BARTS –	HbA+HbH	excess beta chains as tetramers (HBH) result in membrane damage and hemolysis. HbH is also useless for O_2 delivery
Hydrops fetalis (homozygous state)	4	0	fatal at or before birth	>50% BARTS	–	no α-globin synthesised and therefore the condition is incompatible with life

BARTS Hb = tetramers of γ chains

Table 15.17 Beta-thalassemia syndromes

Classification	*β-genotype*	*Anemia/ microcytosis*	*Hemoglobin electrophoresis*	*Comments*
thalassemia maxima	β/β	none/none	HbA_2 < 3.5% HbF<1%	clinically and hematologically normal
thalassemia minima	β/β^+	none/none	slightly ↑ HbA_2 ↑ HbF	
thalassemia minor	β/β^+ (severe) β/β°	mild/mild to moderate	HbA_2 3.5%–7.5%, HbF increase is diagnostic of thalassemia minor	Hb is 2–3 g/dl less than normal; mild microcytosis and hypochromic RBC with poikilocytosis. No evidence of overt hemolysis. The importance of identifying this trait is that when both patients have the trait there is 25% risk of begetting a child with Thal major
thalassemia intermedia	β^+ (mild)/ β^+severe	moderate to severe/moderate to severe	6–8% HbA_2, 20–50% HbF, remainder HbA	jaundice with moderate splenomegaly. Anemia requires transfusion but disease is less severe than thalassemia major
thalassemia major	$\beta^\circ/\beta^\circ\beta^+$ severe/ β^+severe	severe/severe severe/severe	3–11% HbA_2, remainder HbF 3–11% HbA_2, 10–90% HbF remainder HbA	classic transfusion-dependent disease

overbite, malar prominence and depression of the nasal bridge (known as *chipmunk facies*). Moderate hepatosplenomegaly along with lymphadenopathy also develop.

Complications Iron overload causes hepatic fibrosis and cirrhosis as early as the age of five. Deposition of iron in the endocrine organs lead to IDDM, hypothyroidism, hypoparathyroidism and hypopituitarism. Cardiac siderosis progresses to cardiomyopathy which contributes to early mortality.

Investigations Hemoglobin is usually in the range of 2–6.5 g/dl. Hematocrit is between 10–24 per cent. The red blood cell count is 2–-3 million cells/mm^3 of blood. The red cell indices MCV, MCH and MCHC are low.

A peripheral blood film shows hypochromic microcytic red blood cells. There is severe anisocytosis, poikilocytosis and polychromasia. Hypochromic target cells are also seen. RDW (the red cell distribution width) exceeds 20 per cent indicating severe anisocytosis. Closer examination of RBCs reveals basophilic stippling. Alpha tetramers, present within the RBC can be detected by methyl violet. Nucleated RBCs are also a feature of a stimulated marrow. The microcytes have a reduced osmotic fragility. Electrophoretic patterns help confirm the diagnosis of thalassemias. HbA_1 is reduced whereas fetal hemoglobin and HbA_2 are increased.

Other investigations which suggest the presence of an ongoing hemolytic process are

an increase in the reticulocyte count, serum unconjugated bilirubin, decreased haptoglobin and hemopexin; serum iron is increased.

Urinary abnormalities are also noted. An X-ray of the skull shows widening of the diploe due to an expanded marrow. It is described as a *hair on end* appearance.

Treatment Transfusion therapy aims at improving the hemoglobin status. It also prevents the consequences of chronic anemia and hypoxia such as growth failure, extramedullary hematopoiesis, and the cosmetic complications of bone marrow expansion.

Monthly transfusions should maintain the hemoglobin level at 10 g per cent (*hypertransfusion*) When an attempt is made to maintain it at 12 g per cent by more frequent transfusions it is known as *supertransfusion therapy*. When the transfusion requirements increase beyond 250 ml/g/year, splenectomy is planned.

The adverse side effects of excess iron is countered by administration of chelation therapy on a continuous basis. Desferroxamine is the drug of choice at present and is administered by a subcutaneous infusion pump.

Prognosis Thalassemia major is a crippling disease and death occurs before the age of 30 years due to overwhelming sepsis and cardiac failure.

Prevention In certain countries where thalassemia is widely prevalent, antenatal diagnostic measures can be undertaken. The gene frequency in north India is about 5 per cent. In high risk pregnancies trophoblastic tissue is obtained by chorionic villus biopsy at 8–12 weeks. With the help of DNA probes, gene mapping helps to detect the defective genes. Termination of the affected pregnancies have significantly decreased the incidence of this disease.

Sickle Cell Anemia

Sickle cell anemia is an inherited hemoglobinopathy characterised by the presence of a structurally abnormal hemoglobin, hemoglobin S. Hemoglobin S is different from normal adult hemoglobin HbA, in that the glutamic acid residue is replaced by the amino acid valine in the sixth position of the β-globin chain of the peptide due to a gene mutation on chromosome 11.

Inheritance This disorder is inherited as an autosomal codominant trait. In heterozygotes only a proportion (40%) of the total hemoglobin is HbS. They are said to have the *sickle cell trait*. In homozygotes, HbS constitutes 100 per cent of the hemoglobin (sickle cell disease).

Pathophysiology On exposure to low oxygen tension, soluble HbS undergoes polymerisation to form insoluble crystals. This is responsible for the distortion (sickled appearance) and reduced 'plasticity' of the red cells. Various factors influence the sickling tendency of the red blood cells in sickle cell disease. Interaction between HbS and the globin chains of other hemoglobins (like those of HbC, HbD) enhances the sickling tendency. HbS does not interact with fetal hemoglobin (HbF) which explains why sickle cell anemia manifests only after the first five months of life. A low mean corpuscular hemoglobin concentration (MCHC) reduces the risk of sickling, as is seen when HbS is associated with thalassemia. Lastly, an acidic pH can also increase sickling of the red blood cells by increasing the amount of deoxygenated hemoglobin present in them.

Sickled erythrocytes result in the following:

1. Chronic hemolysis occurs due to removal of the sickled cells within the spleen.
2. Vascular occlusion: HbS causes reduced viscosity of blood by enhancing the rigidity of the red blood cells. The reduced elasticity of the RBC is confined not only to the sickled cells but also to normal-looking cells with Hb

Sluggish blood flow results in the worsening of hypoxia which predisposes to more sickling; this is a cyclical phenomenon. The resultant vasoocclusion causes organ infarction. The bones, liver, spleen, brain, lungs and penis are common sites for vascular occlusion.

3. Splenic infarction causes functional asplenia, a factor which predisposes to life-threatening infections with pathogens such as Pneumococcus, *H. influenzae, Salmonella typhi, E. coli* and *Mycoplasma pneumoniae*. Sometimes in young children, and occasionally in adults (in whom the spleen has not undergone autosplenectomy), a sudden pooling of large volumes of blood within the spleen causes hypovolemic shock: a condition known as *sequestration*[1] *crisis*.

4. *Aplastic crisis*: Viral infections and folate deficiency can often cause a transient marrow aplasia in subjects with sickle cell disease. Recovery is heralded by an increase in reticulocyte count and by amelioration of anemia.

5. *Hyperhemolytic crisis* occurs when G-6 PD deficiency coexists with sickle cell anemia. It is precipitated by ingestion of oxidant drugs.

Clinical features The onset of anemia is delayed and the infant is asymptomatic until 3–6 months. Occlusive crisis is the earliest and most common complication of the disease. Painful episodes of ischemic tissue damage last for 5–6 days. Acidosis, dehydration, infections and even stress can precipitate an attack. Cerebrovascular accidents, due to vasoocclusion within the cerebral circulation occur in 5–10% of patients. Neurological deficits like hemiplegia result in a permanent handicap. Older patients suffer from repeated pulmonary infarctions. Multiple episodes of pulmonary infarctions can result in pulmonary hypertension. Painful swelling of the small joints (*hand mouth syndrome*) are a common feature in children. Permanent orthopedic deformities develop in 50 per cent of patients. Sickling of RBCs within the hypertonic environment of the renal medullary tissue can cause renal papillary necrosis, renal tubular concentration defects and renal tubular acidosis. Chronic leg ulcers occur secondary to an underlying vasoocclusive tendency in the limb circulation. *Priapism*[2] due to venous engorgement occurs in five per cent of males. It can produce pain, urinary retention and impotence. Ocular complications of sickle cell disease become clinically significant in early adolescence. *Vasoocclusive crisis* during pregnancy is dangerous for the mother as well as for the fetus.

Sickle cell disease produces a stable hemolytic anemia. However, three types of anemic crisis can cause a dramatic fall in the hemoglobin value: sequestration crisis, aplastic crisis and hyperhemolytic crisis. These have been discussed in the section on pathophysiology of the disease. As a result of chronic hemolysis, pigmentary gallstones have been noted in children as young as three years of age. Progressive impairment of liver function contributes to the clinical icterus in these patients.

Investigations The hemoglobin concentration varies within a range of 6–9 g/dl. The peripheral blood film shows severe normocytic, normochromic anemia, sickle cells, polychromatophilia, occasional nucleated RBCs, red cell fragments and *Howell-Jolly bodies* (indicating hyposplenia). The total leukocyte count is elevated. The reticulocyte count exceeds five per cent.

Sickle cell preparation

Red cells are incubated in vitro with reducing agents such as sodium metabisulphite. The deoxygenated red blood cells undergo sickling and can be visualised under the light microscope. Hemoglobin electrophoresis reveals elevated levels of HbS, HbF and HbA_2, which confirms the diagnosis of sickle cell disease.

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1 Sequester refers to pool.

2 Priapism refers to persistent erection.

Treatment Painful conditions due to vasoocclusive crisis are managed with oral narcotics. Oral hydration is often preferred to intravenous fluid therapy. Oxygen therapy is indicated only if the patient becomes hypoxic. Transfusion with packed cells is given to dilute the patient's blood and to reduce the severity of the vasoocclusive crisis. Patients should have adequate nutrition and should receive folate supplementation. Appropriate antibiotics are indicated whenever there are clinical signs of infection. Drugs which increase expression of HbF may be useful; these include hydroxyurea, 5-azacytidine and butyrate. Drugs which increase solubility of HbS (cyanates, urea) have been tried but are toxic.

Prevention Intrauterine diagnosis of sickle cell disease is now possible by gene mapping of fetal fibroblasts obtained by chorionic villous biopsy. Termination of pregnancy is often advised when sickle cell disease is diagnosed antenatally. Certain tribal populations in the Nilgiris, Central India, Orissa and Bihar have a high prevalence of sickle cell anemia.

Other hemoglobinopathies

Other hemoglobinopathies encountered in India include Hemoglobin E (prevalent in West Bengal, Assam), Hemoglobin D (prevalent in Punjab, Gujarat) and Hemoglobin C.

KEY CONCEPTS

Iron deficiency anemia

- Iron deficiency is probably the most common form of anemia worldwide. The most common mechanism of iron deficiency anemia is blood loss; important causes include GI loss (e.g. hookworm disease, bleeding ulcer) and menstrual loss (in women). Individuals on a cereal-rich meat-poor diet are particularly susceptible to nutritional iron deficiency.
- Iron absorption occurs in the duodenum and upper jejunum and is regulated by the mucosal cells. From the mucosal cell, iron is transferred to transferrin and then enters red cell precursors in the marrow. Iron enters into two pools: a soluble active storage pool of ferritin (~700 mg)) and an insoluble pool of hemosiderin (~300 mg).
- Symptoms in iron deficiency anemia include fatigue, weakness malaise, breathlessness and decreased work capacity. A history of pica is specific for iron deficiency anemia. Physical findings include pallor; specific for an iron deficient state are the findings of koilonychia, and postcricoid pharyngeal webs.
- Usually the clinical findings and the peripheral blood smear picture of a microcytic hypochromic anemia are enough to suspect a diagnosis of iron deficiency anemia. Definitive diagnosis can be established by documenting a low serum ferritin (<12 μg/dl), low serum iron, increased TIBC and an absence of iron on staining of the bone marrow preparation.
- Oral iron therapy (ferrous sulphate 200 mg tid) is sufficient in most cases; reticulocytosis is evident at about 7–10 days after starting therapy. It takes about 4 weeks of therapy to correct the deficiency and a further 4–6 months to replenish bone marrow stores. Parenteral therapy may be rarely required if there is intolerance of oral iron.

Megaloblastic anemia

- It is characterised by defective synthesis of DNA due to either vitamin B_{12} or folate deficiency. Defective DNA synthesis results in normal cytoplasmic maturation but an arrest in nuclear maturation.
- The morphologic hallmark of this is common to cells of all lineages i.e., large cells; erythocytes have an MCV >100 fl, polymorphonuclear white blood cells have hypersegmented nuclei, and platelets also appear large and may have a bizarre shape. The pathophysiologic hallmark is *ineffective erythropoiesis* and intramedullary hemolysis.
- *Causes of vitamin B_{12} deficiency* include a strict vegetarian diet, malabsorption syndrome (tropical sprue, bacterial overgrowth, ileal disease) and

pernicious anemia (autoimmune disease with atrophic gastritis, achlorhydria, and a failure of secretion of gastric intrinsic factor). *Causes of folate deficiency* include inadequate intake, increased requirement (pregnancy, infancy, myeloproliferative conditions), alcohol intake, tropical sprue and drugs (certain anti-cancer drugs, antibiotics, antimalarials).

➢ Symptoms are those of anemia: fatigue, malaise, shortness of breath and palpitations. Atrophic glossitis and presence of neurologic symptoms and signs suggestive of posterior spinal column involvement (subacute combined degeneration of the cord) suggest a diagnosis of pernicious anemia.

➢ Diagnostic features include a peripheral smear picture of pancytopenia with macrocytosis, and elevated LDH levels. Decreased serum vitamin B_{12} levels (<100 pg/ml), reduced serum folate (4 ng/ml) or red cell folate (more specific) confirm the diagnosis. If pernicious anemia is suspected, a Schilling test may help confirm the diagnosis.

➢ Treatment of folic acid deficiency is with oral folate (5 mg tid followed by od) while vitamin B_{12} is replaced by the parenteral route (1000 mg i.m. biweekly initially). Patients with neurologic disease should not be treated with folate alone due to the potential of worsening of neurologic disease.

Glucose-6 phosphate dehydrogenase deficiency

➢ This is an X-linked recessive disorder common in India, the Mediterranean and the African continent. The presence of this disorder protects against falciparum malaria and the defect is common in malarial endemic areas.

➢ Individuals who have erythrocytes with the enzyme deficiency are liable to oxidant stress; drugs (sulpha group, primaquine), fava beans can precipitate hemolytic episodes. Older erythrocytes are more deficient in the enzyme and denatured hemoglobin precipitates as Heinz bodies within them; this results in selective destruction of older red blood cells in the spleen and *bite cells* in peripheral blood.

➢ The clinical picture is one of acute hemolysis and the peripheral blood smear provides additional corroboration of the etiology if Heinz bodies are demonstrated. A definitive diagnosis requires assay of the enzyme in erythrocytes; such measurements must be made during a steady state period as younger red cells are abundant during the acute phase and enzyme estimates at this stage may mask the defect.

Paroxysmal nocturnal hemoglobinuria

➢ PNH is an acquired defect in which a clone of red cells is unable to construct an anchor for attachment of cell membrane proteins; this results in an increased susceptibility to complement-mediated lysis.

➢ The disorder is characterised by chronic hemolysis, reduced platelets, and an increased susceptibility to infections (neutropenia). There is also an increased risk of venous thromboses (Budd-Chiari syndrome). Contrary to the name, hemoglobinuria is uncommon, although hemosiderinuria is common.

➢ The peripheral blood smear shows pancytopenia. The sucrose hemolysis test is a screening test while the acidified serum lysis test (*Ham test*) is confirmatory. Urinalysis reveals hemosiderinuria and leucocyte alkaline phosphatase (LAP) levels are low.

➢ Treatment measures include steroids, folate supplementation, hypertransfusion with washed red cells, and heparin (for thrombotic episodes).

➢ PNH may progress to acute myeloid leukemia in 5 per cent.

Autoimmune hemolytic anemia

➢ AIHA is associated with antibodies to red cell antigens.

➢ These antibodies may be of the warm type (IgG, reactive at 37°C; may be idiopathic, or due to SLE, CLL, lymphomas or drugs) or of the cold type (IgM, reactive at 4°C; causes include PNH, SLE, CLL, mycoplasma, infectious mononucleosis).

➢ AIHA with warm-type antibodies presents with anemia, jaundice, splenomegaly and purpura. AIHA with cold-type antibodies presents with splenomegaly and purpura. AIHA with cold-type antibodies presents with anemia, cold-induced Raynaud's phenomenon and acrocyanosis.

➢ Diagnosis of AIHA is by the direct Coomb's test performed at different temperatures. Supportive evidence of in vivo hemolysis is obtained by demonstrating reticulocytosis, increase in unconjugated bilirubin, LDH and a reduction in haptoglobin.

➢ Warm-type AIHA is responsive to steroids; splenectomy and azathioprine have a role in steroid-refractory cases. Blood transfusions and folate supplementation are important adjuncts. Cold-type AIHA is not responsive to steroids or to splenectomy. The patient is advised to keep warm and blood transfusions are to be avoided as far as possible.

Thalassemia

➢ This is an inherited hemoglobinopathy characterised by a reduced rate of synthesis of α (α thalassemia) or (β thalassemia) globin chains. Unbalanced excessive synthesis of globin chains results; there is an excess of α chains in β thalassemia and vice versa.

- The anemia in thalassemia is related to hemolysis and ineffective erythropoiesis (resulting in extramedullary hematopoiesis).
- **Beta-thalassemia:** since there is one pair of genes which regulates synthesis of the β globin chain, two forms of disease may occur:

  Thalassemia major (homozygous form) results in severe microcytic hypochromic anemia along with hepatosplenomegaly. Marrow hyperplasia results in typical chipmunk facies (frontal bossing; X-ray appearance of widened diploe: *hair on end*).

  Thalassemia minor (heterozygous form) results in mild anemia and is usually asymptomatic.
- **Alpha-thalassemia:** Since there are two pairs of genes that regulate α globin chain synthesis, four forms of the disease may be encountered.

  α-thal trait 2 (one locus affected) is an asymptomatic condition, α-thal trait 1 (2 loci affected) is associated with subclinical hemolysis, while α-thal-Hb H disease (3 loci affected) is associated with clinically evident anemia (β tetramers accumulate). When all four loci are affected, the disorder results in fatal hydrops fetalis (**Hb BARTS** [γ4]).
- Investigations in a patient with suspected thalassemia include peripheral blood smear, Hb electrophoresis and quantitation of individual globin chains. β-thalassemia major is associated with increased HbA_2 (normal 1.5–3%) and Hb F (normal 2–5%). In α-thalassemia, neither HbA_2 nor HbF is increased (deficient α chain synthesis).
- Management of β-thalassemia includes transfusions to maintain Hb >10 g/l and hematocrit >27–30%; desferrioxamine is used concomitantly as an iron chelator to obviate visceral iron overload. Splenectomy is an option if there is hypersplenism.
- α-thalassemia is managed more conservatively. Oxidant drugs should be avoided. Rarely, splenectomy may be considered for HbH disease.

Sickle cell anemia

- In sickle cell anemia, a mutation results in substitution of valine for glutamic acid at position 6 of the globin chain (HbS). The disease is inherited as an autosomal dominant trait. The heterozygous state is called sickle cell trait while the homozygous state is sickle cell disease.
- HbS polymerises into fibrillar aggregates (tactoids) when it is deoxygenated; acidosis, hypoxia, and hypertonicity promote such polymerisation.
- Symptoms are due to hemolysis, vasoocclusive crises and a susceptibility to infections. Chronic hemolysis results in anemia, growth retardation and chronic leg ulceration. Anemia is worsened by aplastic episodes, splenic sequestration and by hyperhemolytic crises.
- Vasoocclusive crises result in pain in the long bones, fingers (dactylitis), and visceral infarction (the retina, nervous system, kidneys and spleen are especially prone). Autosplenectomy results from repeated splenic infarction. There is an increased susceptibility to bacterial sepsis with encapsulated organisms.
- The diagnosis is suspected when sickle-shaped cells appear in the peripheral blood smear; sickling may be induced in vitro by exposing the red cells to 2% sodium metabisulphite. Hemoglobin electrophoresis is confirmatory.
- Management includes avoidance of precipitating factors (such as dehydration), treatment of infections, and transfusions with fresh frozen plasma. Vaso-occlusive crises are managed with proper hydration and analgesics. Pneumococcal vaccination should be administered as a prophylactic measure. Hydroxyurea has been tried as a measure to increase HbF levels. Gene therapy is likely to play an important role in the future.
- Genetic counselling and prenatal detection have an important role in management.

15.5 Disorders of the coagulation system

Platelet Disorders

Most disorders of platelets occur as a result of a decreased platelet count. *Thrombocytopenia* is defined as a platelet count of less than 100,000/μl. Bleeding attributed to a deficiency of platelet number is known as *thrombocytopenic purpura.*

Thrombocytopenia can occur due to decreased production of platelets, decreased survival (or increased destruction), sequestration within an enlarged spleen and, dilution following large volume blood transfusion.

The common causes are shown below. The relationship between platelet count and clinical bleeding is depicted in Table 15.18.

Causes of thromobocytopenia

1. Decreased production of platelets
   Generalised diseases of the bone marrow
   - Aplastic anemia: congenital and acquired
   - Marrow infiltration: leukemia, disseminated cancer

   Selective impairment of platelet production
   - Drug-induced: alcohol, thiazides, cytotoxic drugs
   - Infections: childhood rubella

   Ineffective megakaryopoiesis
   - Hereditary: Wiskott-Aldrich syndrome
   - Acquired: megaloblastic anemias

2. Decreased platelet survival
   Immunologic destruction
   - Idiopathic thrombocytopenic purpura, SLE
   - Isoimmune: posttransfusion and neonatal
   - Drug-associated: quinidine, heparin
   - Infections: infectious mononucleosis, HI infection

   Increased consumption
   - Disseminated intravascular coagulation
   - Thrombotic thrombocytopenic purpura
   - Giant hemangiomas
   - Microangiopathic hemolytic anemias
3. Sequestration
   - Hypersplenism
4. Dilutional: massive transfusion

Acute idiopathic thrombocytopenic purpura

Acute idiopathic thrombocytopenic purpura (ITP) is the commonest of the thrombocytopenic purpuras affecting children.

Etiopathogenesis It is an immunologically-mediated disorder. Viral infections like upper respiratory infections, hepatitis, rubella and mononucleosis often precede the illness by two to four weeks. Antibodies directed against these viral antigens form complexes which are adsorbed on the platelet surface. The affected

Table 15.18 Relation between platelet count and bleeding

Platelet count	*Clinical findings*
>100,000/μl[1]	none
40,000–1,00,000/μl	prolonged bleeding time abnormal clot retraction, no significant petechiae or purpura
10,000–40,000/μl	petechiae, easy bruisability and epistaxis
<10,000/μl	major risk of bleeding

[1] 1 μl = 1 mm^3

platelets are prone to premature destruction by the mononuclear-phagocyte system. Currently, no reliable serologic test exists to confirm the diagnosis of idiopathic thrombocytopenic purpura. The association of ITP with immunohemolytic anemia is called *Evan syndrome.*

Clinical features Acute onset of bruising, generalised petechial rash, nose bleeds and hemorrhagic bullae of the gums and lips in a normal child are the commonest presenting features of the disease. Gastrointestinal and genitourinary hemorrhages occur in severe thrombocytopenia. Intracranial bleeding is a dreaded complication and occurs only in a few patients. Except for the signs of bleeding, the patient usually has no enlargement of the liver, spleen or lymph nodes. Presence of marked splenomegaly should alert the physician to look for some other cause of thrombocytopenia. The tendency to bleed lasts for one to two weeks and complete recovery occurs in about three months. Occasionally, the disease takes a chronic course and may last for several years.

Investigations The peripheral smear shows a paucity of platelets. The platelet count is reduced to below 20,000/µl. The few platelets seen in the smear are large (giant platelets). A bone marrow aspirate reveals increased megakaryocytosis. The other cell lives are normal. The bleeding time is prolonged, but the clotting time is normal. An abnormal bleeding time is no contraindication to a bone marrow aspiration.

Treatment No specific therapy is needed for most patients with ITP. Normal platelet counts are regained within 3–12 months. The result of severe spontaneous bleeds particularly into the cranial cavity is high in the initial phase of the disease. Only such patients require fresh blood or platelet transfusion. Steroids in a dose of 1–2 mg/kg/24 hours in divided doses reduces the severity and shortens the duration of the acute phase of the disease. Therapy is continued unti platelet counts normalise and is then tapered. I thrombocytopenia persists beyond three week in spite of steroids, tapering of the drug i advised since it is unlikely that improvement wil occur with intake of this drug. Intravenou gammaglobulin (2 g/kg) also induces remissio in many cases of acute and chronic ITI Splenectomy is performed only when a lo platelet count is present for more than one yea (chronic ITP).

Chronic idiopathic thrombocytopenic purpura
Chronic ITP occurs in women between 20–4 years of age.

Pathophysiology Platelet-associated immuno globulin (PAIgG) belonging to the IgG clas have been detected in 90 per cent of patient with chronic ITP. These coat the platelets whic are eliminated by the mononuclear phagocyti system within the spleen.

Clinical features This disease is often brough to notice by petechial lesions. Occasionally th diagnosis is made when a routine blood fil reveals a low platelet count. The spleen usually not enlarged. Since ITP is often th presenting manifestation of SLE, lymphom AIDS and Evan syndrome, the presence of thes diseases should not be ignored.

Investigations Thrombocytopenia with platelet count of 25,000–75,000/µl and th demonstration of platelet antibodies a confirmatory of the disease. The bone marrow cellular with increased megakaryocytopoiesis.

Treatment Steroids 60–80 mg/day form th mainstay of medical treatment. Splenectomy useful when steroid toxicity or dependenc develop. Intravenous gammaglobulin (2 g/kg anti Rh(D) globulin (50 µg/kg in Rh positiv individuals) or oral danazol have also been use with success.

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytic purpura (TTP) is characterised by 1) severe thrombocytopenia, 2) microangiopathic hemolytic anemia, 3) fever, 4) CNS disturbances, and 5) renal diseases.

Etiopathogenesis It is not very clear. Severe endothelial damage causes thrombi formation which block arterioles and capillaries in various parts of the body.

Clinical features A sudden onset of pallor, petechiae, convulsions and coma in an apparently healthy adult is a common presenting feature of this rare disease.

Investigations No single investigation is diagnostic of TTP. The peripheral smear shows fragmented RBCs, marked polychromatophilia and severe thrombocytopenia. Renal function tests may be abnormal.

Treatment Steroids, plasmapheresis and plasma infusions have been used to induce long-term remissions.

Hemophilia

Hemophilia is an X-linked recessive disorder in which deficiency of a coagulation factor causes excessive bleeding. Hemophilia A results from deficiency of factor VIII. Hemophilia B results from deficiency of factor IX. Although clinically indistinguishable, correct diagnosis is essential as the treatment of the two disorders differs.

Genetics The mode of inheritance is X-linked recessive. Eighty per cent of patients may give a family history of the disease. In 20 per cent of patients, however, spontaneous mutation results in this disorder.

All the sons of a hemophiliac male and a normal female will be normal and all their daughters will be carriers. When these carrier daughters have children with normal men, their sons stand an equal chance of being normal (50%) or having hemophilia (50%) and their daughters an equal chance of being normal (50%), or being a carrier (50%).

Daughters of an affected male and a carrier female can also have hemophilia. With such parents, each daughter has a 50:50 chance of inheriting the disease, and a 50:50 chance of being normal.

Pathophysiology The severity of bleeding in both types of hemophilia depends on the amount of factor VIII or IX present in the plasma. Factor VIII comprises of two fractions. In hemophilia A, the low molecular weight *procoagulant fraction* is decreased but *von Willebrand's factor* level is normal. The level of factor VIIIc or factor IX in hemophilia is reduced to 0.05 per cent (normal level for each is 0.5–1.1 units/ml, also defined as 50–110 per cent). Table 15.19 shows the relation of factor VIII levels in blood to the severity of hemophilia.

Clinical features Although the deficiency is present at birth, the bleeding does not usually occur in the first few months of life. In moderately affected cases, the disorder may be brought to notice due to a hemorrhagic cephalhematoma, prolonged bleeding following circumcision, or a hematoma following intramuscular injections of vitamin K or DPT immunisation. As the infant starts crawling, bleeding is noted in the scalp and limbs. Easy bruising and prolonged bleeding following minor injury also occurs. In severely affected infants, hemorrhage into the joint spaces (hemarthroses) results in swelling, pain and limitation of movement. Hemarthroses is pathognomonic of hemophilia. Repeated joint bleeds may result in osteoporosis, muscle atrophy and a fixed 'frozen' joint. Spontaneous gastrointestinal bleeds and hematuria are also quite common. Although spontaneous intracranial hemorrhage is unusual, life-threatening intracranial bleeds can occur following even minimal head trauma.

Hemophilia carriers are not susceptible to spontaneous bleeds but may suffer from prolonged, posttraumatic and postsurgical hemorrhage.

Investigations The bleeding time is normal but activated partial thromboplastin time (APTT) is abnormally prolonged in hemophilia A and B. A plasma assay shows a low factor VIII procoagulant activity and normal levels of VWF in hemophilia A. In hemophilia B, a low factor IX level is confirmatory.

Treatment

Preventive measures: Prevention of trauma is of great importance in the management of a hemophiliac subject. Ideally, the play area of a child should be padded and a child learning to walk is supervised. Contact sports are usually avoided. Intramuscular injections should not be given. Aspirin and NSAIDs (which affect platelet function) are strictly contraindicated. Acetaminophen (paracetamol) is the drug of choice for pain relief. Since hemophiliacs have an increased access to blood products, hepatitis B vaccine should be administered during infancy (3–6 months of age).

Replacement therapy: When bleeding occurs, coagulation factor replacement therapy is essential to prevent exsanguination, pain and disability. Factor VIII is used to secure hemostasis in hemophilia A and factor IX concentrate in hemophilia B.

A good source of factor VIII concentrate is *cryoprecipitate*, a single bag of which contains 80–90 units of factor VIII. One bag of cryoprecipitate per 5 kg body weight will raise the level of factor VIII to 50 per cent of normal. To reduce the risk of AIDS, cryoprecipitate is now being produced from single units of blood which have been screened for HIV.

Commercial preparations of pure factor VIII are also available. They are dispensed as lyophilised powders which can be reconstituted by the patient himself and administered at home. In emergency situations, where cryoprecipitate is not available, fresh frozen plasma is an effective alternative; 10–15 ml/kg every twelve hours maintains plasma levels of factor VIII at 10–25 per cent of normal.

In hemophilia B, bleeding is controlled only when fresh frozen plasma or factor IX concentrate is administered. Factor VIII concentrate and cryoprecipitate are ineffective.

In minor non-traumatic bleeds, the deficient factor level (VIII or IX) is raised to 40 per cent. In major bleeds following head injury, and in severe joint and intramuscular bleeds, the factor level is elevated to 60 per cent. Prior to surgical procedures, the factor level is maintained at 100 per cent, and at 40 per cent for at least five postoperative days.

Hemarthroses is a major debilitating feature of the disease. Prior effective replacement therapy, application of cold packs and pressure to the joint, immobilisation of the joint and passive physiotherapy within 48 hours of the bleed help prevent joint stiffness and deformity to some extent.

Table 15.19 Relations of factor VIII plasma levels to clinical severity of disease

Factor VIII plasma level (units/ml) (% normal)	*Degree of severity of deficiency*	*Type of bleeding*
0.5–1.1 (50–110%)	normal	nil
0.05–0.5 (5–50%)	mild	tendency to bleed after moderate trauma
0.01–0.05 (1–5%)	moderate	severe bleeding after mild injury
<0.01 (0–1%)	severe	spontaneous bleeding into muscle and joints

Other treatment modalities in hemophilia: DDAVP (1-desamino-8-D-arginine vasopressin) is a synthetic nonapeptide analogue of pituitary vasopressin. Patients with mild or moderate hemophilia A respond to DDAVP with a significant increase in plasma procoagulant levels. The recommended dose is 3 mg/kg over 15 minutes. This drug can be administered prophylactically prior to dental extractions. EACA (Epsilon amino caproic acid) inhibits fibrinolysis in the oral cavity. It can also lessen the need for factor replacement in patients undergoing dental extraction. Prior to the procedure, cryoprecipitate is infused, followed by 5 grams of EACA. Thereafter, 5 grams of EACA is given every six hours for the next seven days.

Therapy for factor VIII inhibitors: Ten per cent of patients with hemophilia A develop antibodies which inhibit factor VIII. Hemophilia B rarely develops factor IX inhibitors.

The presence of inhibitors prevents the patient from achieving therapeutic levels of factor VIII. Immunosuppressive agents like cyclophos-phamide and steroids are not effective. In order to overcome the effects of these inhibitors, activated prothrombin complexes are being tried. These complexes enter the coagulation cascade distal to the step involving factor VIII inhibitors.

Prognosis Hemophilia is a chronic disease complicated by the risk of developing hepatitis, AIDS and chronic liver disease. Management of the patient requires team effort involving the pediatrician (in the case of a child), orthopedician, hematologist, geneticist and physiotherapist.

Prenatal diagnosis Each male fetus of a carrier mother has 50 per cent risk of having the disease. Prenatal diagnosis is possible through examination of the blood of a male fetus by fetoscopy. If factor VIIIa (VWF) is higher than factor VIIIc level, the presence of hemophilia in the fetus is confirmed. Earlier diagnosis is possible by chorionic villus biopsy, chromosomal analysis of amniotic fibroblasts using DNA recombinant technology enabling identification of the defective gene.

Disorders of Vitamin K-dependent Coagulation Factors

Vitamin K, also known as naphthoquinone, is required for the synthesis of blood coagulation factors II, VII, IX and X. Four other plasma proteins C, S, M and Z are also dependent on the presence of vitamin K.

Vitamin K is a cofactor for the hepatic microsomal enzyme carboxylase which converts the glutamyl residues in the precursor clotting protein to gamma-carboxy glutamate residues (gla). Addition of the gla residue enables the clotting protein to interact with phospholipids in the presence of ionic calcium, in order to generate thrombin. The function of protein C has been discussed earlier. It is a naturally occurring, circulating anticoagulant whose anticoagulant properties are enhanced by another protein, protein S. The function of coagulation proteins Z and M is not yet clear. In the absence of vitamin K, clotting factors lacking the carboxylated residues circulate but are not functional proteins. They are referred to as *proteins induced in vitamin K absence* (PIVKA).

Vitamin K is synthesised by the microflora in the gut. However, this source of vitamin K is by itself insufficient and dietary sources of vitamin K are necessary to meet the requirements of the body. Plants and vegetables are rich sources of vitamin K. The neonate, particularly the small-for-gestation preterm baby, is especially vulnerable to the effects of vitamin K deficiency. Breast milk is a poor source of vitamin K. Conditions resulting in vitamin K deficiency (besides the newborn period) are chronic liver disease, malabsorption syndromes and the intake of anticoagulant drugs.

Clinical features Bleeding from the umbilicus (in neonates), ecchymoses, gastrointestinal bleeding, hematuria, and hematomas are some of the common presenting features of vitamin K deficiency.

Investigations Prothrombin time and APTT are characteristically prolonged.

Treatment Vitamin K when administered either intramuscularly or intravenously relieves the bleeding tendency promptly except in the case of chronic parenchymal liver disease.

von Willebrand's Disease

This disease is an inherited bleeding disorder, characterised by a deficiency of, or a defective vonWillebrand's factor.

Physiology Factor VIII is a complex comprising of two separate protein moieties:
1 Factor VIIIc, which participates in the coagulation cascade, is responsible for the activation of factor X. It is also called factor VIII *procoagulant protein*. The liver is the major producer of this protein.
2. von Willebrand factor (VWF) is a protein synthesised both by the endothelial cells and the megakaryocytes. It is a protein made up of a series of high molecular weight multimers. Its main function is to facilitate adhesion of platelets to subendothelial collagen (nature's gum), thus enabling the formation of a platelet plug. Assessment of the von Willebrand's factor is performed by *Ristocetin[1] platelet aggregation* (RIPA) *test*. Thus, though the two parts of factor VIII are manufactured separately and have different functions, they circulate together as a single unit and help in the proper functioning and interaction of both arms (platelet and coagulation factor) of hemostasis.

[1] Ristocetin is an antibiotic compound which has the peculiar property of attaching to the platelet and activating the von Willebrand factor receptors on the platelet's surface. This leads to platelet aggregation. In the absence of VWF, platelet aggregation fails to occur.

Genetics This disorder is inherited as an autosomal dominant disorder. The gene for the VWF is on chromosome 12.

Pathophysiology von Willebrand's disease is characterised by reduced levels of VWF. Factor VIII concentration in plasma is also low. Strangely, in this disorder, only the clinical features of platelet dysfunction become manifest. Effects of factor VIII deficiency such as bleeding into joints are relatively rare except in severely affected patients, that is, homozygous subjects.

Clinical features The disease manifests during childhood. Easy bruisability, mucosal bleeds (such as epistaxis, gum bleeds) and gastrointestinal hemorrhage are common presenting features. Affected women frequently report menorrhagia. Prolonged bleeding occurs after injury, but hemarthroses are rare.

Investigations A peripheral blood smear shows normal platelet morphology and the platelet count is also within the normal range. The bleeding time is prolonged. Demonstration of low levels of VWF and factor VIIIc procoagulant protein and the absence of RIPA are confirmatory of this disease.

Treatment Infusions of normal fresh frozen plasma or of cryoprecipitate correct the VWF deficiency. In mild and moderate cases of the disease, a synthetic analogue of vasopressin, has been found to be useful in controlling the bleed by increasing VIIIc and VWF levels and by correcting RIPA test abnormality.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a syndrome of diverse etiology characterised by extensive clotting within the vascular tree and its attendant risk of bleeding.

Etiology DIC is caused by several conditions which can activate the coagulation system in a

relatively uncontrolled fashion. The causes are listed in Table 15.20. In our country, septic abortions, burns, snake bites, abruptio placentae and infections are the principal causes of DIC. DIC may be an acute or a chronic process. Acute DIC is common, whereas chronic DIC is a rare condition.

Pathophysiology and clinical features DIC occurs due to release of tissue factor either as a consequence of tissue damage or as a result of endothelial injury. Infections associated with endotoxemia can cause DIC due to multiple mechanisms; endothelial injury and direct activation of the Hageman factor (factor XII) are two such mechanisms. The formation of microthrombi within the vascular tree results in two important effects: firstly, platelets and coagulation factors are consumed (hence, DIC has also been termed *consumption coagulopathy*), and secondly, there is secondary activation of plasminogen resulting in a systemic fibrinolytic state. The fibrin and fibrinogen of the microthrombi are digested by plasmin, but often hyperplasminemia exceeds that required to merely lyse the formed clots; the result is digestion of normal fibrinogen and formation of fibrin-split products, X,Y,D, and E. Since these fibrin degradation products lack a complete structure necessary for normal clotting, a bleeding tendency often dominates the clinical picture. DIC can range in severity from a mild subclinical abnormality in laboratory tests of platelet and coagulation function to a florid clinical picture of excessive bleeding.

Clinically, the manifestations of DIC are related to the visceral thrombosis and the systemic fibrinolytic state, and the features of the primary event (such as snake bite or septic abortion) which initiates the process. The widespread clotting within the circulation has two effects: there is evidence of visceral ischemia and there is damage to circulating red blood cells as they pass through the circulation. Visceral ischemia can manifest as renal, hepatic, pulmonary and cerebral dysfunction. Renal cortical necrosis may supervene and result in renal failure. Thrombosis of the digital vessels can result in acrocyanosis, and gangrene of the distal portion of the extremities. Damage to circulating red cells results in a microangiopathic hemolytic anemia. As mentioned previously, a bleeding tendency results from the consumption of platelets and coagulation factors and is compounded by the presence of fibrin-split products. The bleeding tendency dominates the clinical picture. Bleeding from mucosa and venipuncture sites is common in acute DIC and can be uncontrolled. Gastrointestinal bleeding, pulmonary bleeding and vaginal bleeding can occur. Postinfectious DIC can result in *purpura fulminans*. Chronic DIC manifests as recurrent petechiae or recurrent phlebitis.

Investigations Thrombocytopenia and fragmented red blood cells are noticed on examination of the peripheral blood smear. The prothrombin time, thrombin time and partial thromboplastin time are all prolonged. Fibrinogen levels are reduced and levels of fibrin-degradation products are elevated. Other investigations may be abnormal depending on the nature of the underlying illness (elevated white cell count in sepsis, leukemia; intra-erythrocytic parasities in malaria; hematuria in acute glomerulonephritis and hemolytic uremic syndrome).

Treatment The underlying disorder must be aggressively treated (this includes chloroquine for malaria, removal of retained fetal products in intrauterine fetal death with retention of products; antibiotics for sepsis and antivenin for snake bite). Bleeding tendencies are treated with fresh frozen plasma (to replace coagulation factors) and platelet concentrates (to replace platelets). Thrombotic manifestations like acrocyanosis or digital gangrene require careful use of heparin.

Anticoagulant therapy

Traditionally, anticoagulation is initiated with parenteral administration of heparin simultaneously oral anticoagulants are started. Over a period of 4–7 days, the effect of the oral anticoagulants sets in and then the intravenous heparin can be stopped. The patient is then continued on oral anticoagulants for a variable duration based on the underlying disease. Heparin inhibits thrombin formation by activating antithrombin III. Intravenous heparin is usually administered either as a continuous infusion of 1000 units per hour or as intermittent boluses of 5000 units every six hours. The partial thromboplastin time is monitored during heparin treatment and maintained at 1.5 to 2 times the control. Lower doses of heparin are used in patients requiring prophylaxis of deep venous thromboses (5000 units twice daily). Potential complications of heparin include bleeding, thrombocytopenia (1 in 10 patients) and osteoporosis (only on prolonged usage beyond two months).

Recently, low molecular heparin derivatives have been used for anticoagulation instead of standard heparin. These derivatives have an antithrombotic efficacy similar to heparin but can be administrated subcutaneously, do not require monitoring and are associated with fewer side effects. The precise indication of these agents is likely to become clearer in the near future.

The coumarin derivatives are the most commonly used group of oral anticoagulants and act by preventing reduction of vitamin K epoxides (including a state analogous to vitamin K deficiency). The prothrombin time is used to monitor the effect and adjust the optimal dose. Since the potency of the thromboplastin reagent used by various laboratories varies, a system of standardisation of the anticoagulation level has been developed. The term *International Normalised Ratio* (INR) is used to denote '{prothrombin time of patient/prothrombin time of control}^{ISI}. ISI refers to the international sensitivity index which compares the sensitivity of the thromboplastin used in a particular laboratory to that of a known reference standard. The ideal INR for chronic anticoagulation varies from 1.5 to 2.5; it may vary depending on the underlying indication since certain conditions require a greater degree of anticoagulation than others.

Table 15.20 Causes of disseminated intravascular coagulation

A. Release of procoagulant substances

1. Obstetric conditions
   - septic abortion
   - abruptio placentae
   - amniotic fluid embolism
2. Snake bite
3. Tissue damage
   - burns
   - gunshot wounds
4. Neoplasms
   - acute promyelocytic leukemia
   - mucinous adenocarcinomas
5. Infections
   - gram-negative sepsis
   - malaria
   - rickettsial diseases

B. Contact of cells with damaged endothelium

1. Acute glomerulonephritis
2. Transfusion reaction
3. Extracorporeal circulation
4. Organ grafts

KEY CONCEPTS

Thrombocytopenia

➢ The normal platelet count varies from 150–350 x 10^9/ L. Thrombocytopenia may be due to decreased production (aplasia, infiltration, myelosuppression), reduced platelet survival (ITP, SLE, drugs) or platelet loss (hemorrhage).

➢ The bleeding time is prolonged when the platelet count is <100 x 10^9/L. The risk of bleeding increases when the platelet count is <50 x 10^9/L and spontaneous bleeding is likely with counts below 20 x 10^9/L.

➢ A bone marrow examination differentiates reduced production (absent or reduced megakaryocytes)

from the other mechanisms which may result in thrombocytopenia.

Idiopathic thrombocytopenic purpura

- ITP is a result of immune-mediated platelet destruction; IgG anti-platelet antibodies play a key role in this process. An acute form of disease occurs in children while a chronic variant is more common in adults.
- Clinical features include skin bleeds (petechiae, ecchymoses, purpura), mucosal bleeds (epistaxia, gastrointestinal tract, hematuria) and visceral bleeds (intracranial). The spleen is not palpable in ITP (palpable spleen mitigates against the diagnosis of ITP). A careful history of drugs is important to differentiate it from drug-induced thrombocytopenia.
- Bone marrow examination reveals thrombocytopenia with an increased or normal number of megakaryocytes.
- The natural history of ITP may be variable. Remissions are common in children (attacks last 4–8 weeks typically) while adults have a more chronic relapsing-remitting course. Treatment modalities include measures to protect from trauma, use of steroids, splenectomy (with vaccination against pneumococci), immunosuppressive agents, danazol and intravenous IgG.

Hemophilia

- Hemophilia can be of two types. The more common type A is due to a deficiency of the procoagulant part of coagulation factor VIII. Type B disease is one-tenth as common and is due to a deficiency of coagulation factor IX. Both are X-linked recessive diseases, that is, carried by females and manifested in males.
- When factor VIII levels are more than 5% of the normal levels, the disease may manifest only after major trauma and after surgery. Levels of 1–5% are associated with bleeding after minor trauma. Levels of <1% are associated with severe spontaneous bleeding.
- Bleeding in hemophilia is often deep-seated; hemarthroses, intramuscular, retroperitoneal, intra-abdominal and intracranial bleeds are common when the factor VIII levels are very low.
- Laboratory investigations reveal a prolongation of APTT with a normal PT/BT. Specific factor assay is required for diagnosis and to distinguish type A from type B.
- Treatment consists of avoiding trauma, increasing factor VIII levels with cryoprecipitate, freeze-dried factor VIII concentrates (t $^1/_2$ is 8 hours). Other agents which may be useful include oral antifibrinolytics and DDAVP. Factor VIII inhibitors may develop and complicate the disease.
- Antenatal diagnosis is possible and genetic counselling is important.

von Willebrand's disease

- This is an autosomal dominant disease characterised by a defective adhesion of platelets to the endothelium. The basic defect is a decrease in the antigenic component of factor VIII.
- The clinical hallmark is the occurrence of both platelet-type and coagulation-type of bleeding in an individual with a family history of similar disease. Skin and mucosal bleeds (petechiae, ecchymoses and purpura) are more common than hemarthroses.
- Laboratory tests reveal an increased bleeding time, a poor aggregation of platelets on exposure to ristocetin, and a reduced factor VIII^{AG} (on rocket electrophoresis).
- Treatment includes fresh frozen plasma, cryoprecipitate, factor VIII concentrates, DDAVP and EACA (the latter to suppress fibrinolysis).

Disseminated intravascular coagulation

- DIC is a condition in which coagulation and fibrinolysis occur simultaneously in the circulation.
- DIC may be the result of activation of the intrinsic coagulation pathway (endothelial injury: gram negative sepsis, malaria, heart-lung bypass, transfusion incompatibility; snake venom) or the consequence of activation of the extrinsic pathway due to entry of tissue thromboplastins into the circulation (obstetric causes: abruptio placentae, eclampsia, intrauterine death, amniotic fluid embolism; malignancy: leukemia, carcinomatosis; trauma).
- In acute DIC the bleeding tendency dominates the clinical picture; it clinically manifests as bruising and excessive oozing from mucosa and venipuncture sites. In chronic DIC, thrombotic manifestations may predominate.
- Laboratory tests of coagulation show widespread abnormalities: thrombocytopenia, red cell fragmentation, increased PT, increased APTT and TT, reduced fibrinogen and increased fibrin degradation products.
- Management of DIC includes treatment of the underlying causes, supportive measures (oxygen, volume replacement with fluids), replacement of coagulation factors (fresh blood, cryoprecipitate, platelets); rarely, antifibrinolytic agents, or heparin (for thrombotic features) may be used.

15.6 Disorders of bone marrow failure

Aplastic Anemia

Aplastic anemia is defined as pancytopenia (anemia, leukopenia and thrombocytopenia) resulting from aplasia of the bone marrow.

Etiopathogenesis (Table 15.21) The commonest cause of aplastic anemia includes exposure to drugs and chemicals. The drugs usually implicated in marrow failure are chloramphenicol, phenylbutazone, alkylating agents, antimetabolites, gold and thiouracil. Marrow failure also follows a high dose of total body irradiation, such as in the case of exposure to nuclear explosions and in nuclear plant accidents. Certain infections, especially viral infections, are injurious to the hematopoietic stem cells and can lead to bone marrow aplasia. A rare familial form of aplastic anemia, Fanconi's anemia, presents very early in life with marrow hypofunction and its attendant complications.

Besides, the factors mentioned above, aplastic anemia can also occur without an identifiable cause. These are grouped together as 'idiopathic' aplastic anemia. The precise mechanism by which the myelotoxic factors cause stem cell injury has not yet been clearly understood. It is thought that T cell derived cytokines are involved in the regulation of normal hematopoiesis as there is growing evidence to support this hypothesis. It is possible, therefore, to postulate that marrow failure may result from immunological-mediated suppression of hematopoiesis.

Table 15.21 Major causes of aplastic anemia

A. Acquired
- I. **Idiopathic**
  - Primary stem cell defect
  - Immune-mediated
- II. **Chemical agents**
  - Dose-related
    - Alkylating agents
    - Antimetabolites
    - Benzene
    - Chloramphenicol
    - Inorganic arsenicals
  - Idiosyncratic
    - Chloramphenicol
    - Phenylbutazone
    - Organic arsenicals
    - Methylphenylethylhydantoin
    - Streptomycin
    - Chlorpromazine
    - Insecticides such as DDT, parathion
- III. **Physical agents** (whole-body radiation)
- IV. **Viral infections**
  - Non-A, non-B hepatitis
  - CMV infections
  - EBV infections
  - Herpes varicella-zoster
- V. **Miscellaneous**
  - Infrequently, many other drugs and chemicals

B. Inherited
- Fanconi's anemia

Thymomas are associated with pure red cell aplasia.

Incidence Aplastic anemia affects both sexes and occurs in all age groups.

Clinical features The initial manifestation depends on which cell line is predominantly affected. Progressive pallor, fatigue and dyspnea result from anemia. Thrombocytopenia causes petechiae and mucosal bleeds. Granulocytopenia leads to severe recurrent infections. Splenomegaly is characteristically absent in aplastic anemia. If it is present alongwith lymphadenopathy, bone tenderness and other features of marrow failure, a hematopoietic malignancy is to be excluded. Hypoplasia of the radii and short stature point towards *Fanconi's anemia*. Non-hematopoietic disorders such as chronic renal failure, tuberculosis and hypothyroidism can secondarily cause marrow failure and clinical evidence of these diseases should be sought.

Investigations Aplastic anemia is diagnosed on demonstration of a normocytic normochromic anemia, pancytopenia, a low reticulocyte count in the peripheral blood film, and hypoplasia of the bone marrow on examination of a bone marrow biopsy specimen. Pancytopenia occurs in the inital stages of '*aleukemic leukemia*' and myelodysplastic syndromes, and these disorders can be confused with aplastic anemia. A bone marrow aspirate study reveals hypercellularity with excess immature myeloid cells in hematopoietic malignancies. Occasionally, pancytopenia with immature erythroid and myeloid cells (*leukoerythroblastic picture*) may be seen in the smear. The bone marrow, in such cases, is populated by tumour cells (multiple myeloma, lymphoma, neuroblastoma). This is known as myelophthisic anemia. Its importance lies in the fact that treatment varies with the different marrow failure syndromes. Endocrine studies, renal function tests and a search for a tuberculous focus also form part of the work-up of a patient with suspected aplastic anemia.

Treatment In cases of drug-induced aplasia, withdrawal of the toxic drugs often leads to recovery of bone marrow function. Supportive therapy in the form of blood transfusion is sufficient. Idiopathic aplastic anemia is, however, more diffcult to treat. In a young patient (less than 50 years of age), where an HLA-matched donor is available, early allogenic (BMT) bone marrow transplantation is curative. Blood transfusions should be avoided in such patients, since sensitisation to the non-HLA antigens in the potential donor cells might occur. In older patients, where HLA matched donors are not available, immunosuppressive therapy with intravenous antithymocyte globulin (40 mg/kg/day for 4 days) and methyl prednisolone (10–20 mg/kg/ day for 2 weeks), is helpful. Androgens, blood cell component therapy and antibiotics are also useful in the management of these patients. In patients who have been diagnosed to have an associated thymoma, thymectomy has been found to be of great benefit in curing the disease.

Prognosis When granulocytes are less than 0.5 x 10^9/L, platelets less than 20 x 10^9/L, reticulocyte count less than 1 per cent and the bone marrow is hypocellular with more than 70 per cent non-myeloid cells, the aplasia is considered to be of a severe nature. Such patients may succumb to the illness within 6–8 months unless treated.

BONE MARROW TRANSPLANTATION

Pluripotent stem cells, when infused into a patient suffering complete marrow ablation, are capable of reconstituting normal lympho-hematopoiesis (Fig 15.13).

Principles involved in BMT

Malignancies: Standard regimens using radiotherapy and chemotherapy not only eradicate

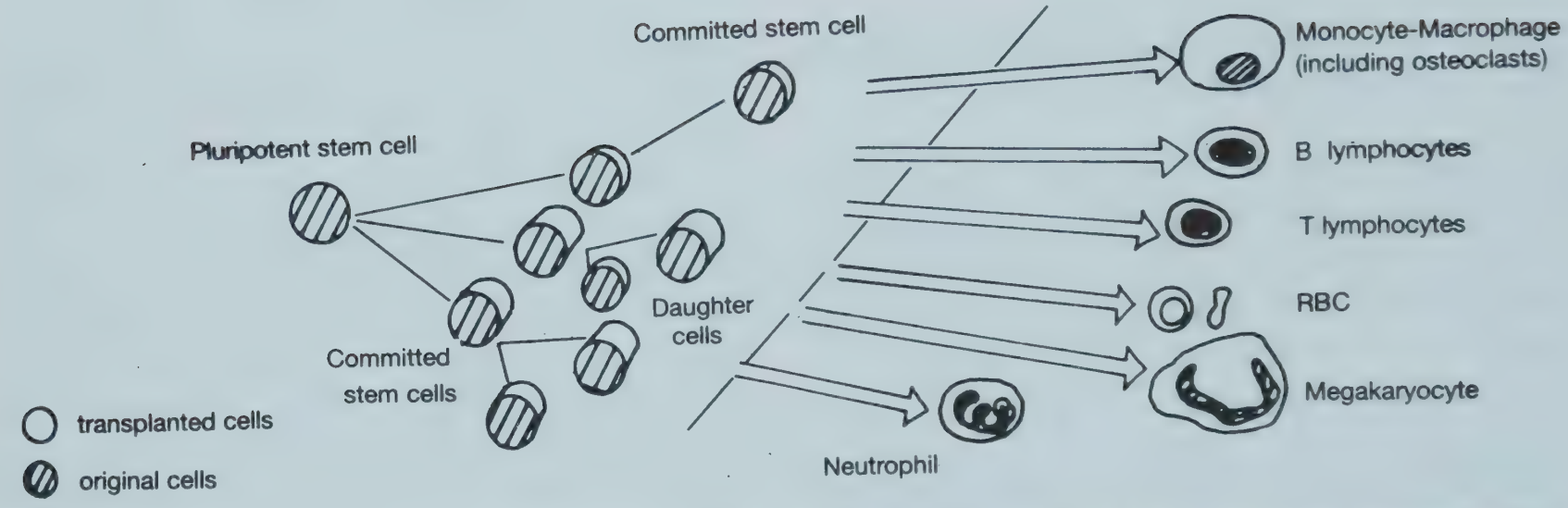

Fig 15.13 Bone marrow transplantation replaces defective stem cells with disorder in hematopoietic, immunological and metabolic function with normal stem cells

the malignancy but also destroy the hematopoietic elements within the marrow. BMT permits the safe use of higher doses of cytotoxic drugs necessary for effective tumour ablation. Further more, allogenic BMT confers an immunologic advantage: donor cells recognise and destroy residual malignant cells by 'graft versus leukemia' effect.

Aplastic anemia: BMT replaces defective stem cells which have lost the ability of hematopoiesis by normal totipotent cells.

Inherited metabolic disorders: Transplanted stem cells are capable of generating a large mass of cells which occupy the whole reticulo-endothelial system. Thus, it is possible to use transplanted marrow as a source of a missing or defective enzyme in lysosomal enzyme defects (Fig 15.14).

Congenital bone marrow disorder: In some congenital immune disorders, the defective stem cells are incapable of producing cells responsible for normal defence mechanisms such as antibody production or phagocytosis. With BMT it is possible to replace defective cells with stem cells capable of normal immune function.

Indications for BMT

I Malignancies
- A. *Leukemia*
  - ALL - poor risk in first remission
  - WBC < 100 X 10^9/L
  - ALL relapse in second remission
  - AML - first remission
  - CML - chronic phase
  - hairy cell leukemia
- B. *Solid tumours:* Hodgkin's disease, Wilm's tumour, Ewing's sarcoma, Burkitt's lymphoma

II Aplastic anemia: acquired aplastic anemia, Fanconi's anemia

III Inherited metabolic disorders: Gaucher's disease, Nieman-Pick's disease, glycogen storage disorders, mucopolysaccharidoses and leukodystrophies

IV *Disorders of individual cell lines*
- A. *Red cell disorders*: thalassemia, sickle cell anemia
- B. *Neutrophil disorders:* chronic granulomatous disease, Chediak-Higashi syndrome.
- C. *Platelets:* severe Glanzman's disease.
- D. *Congenital immune disorders:* severe combined immune deficiency syndromes

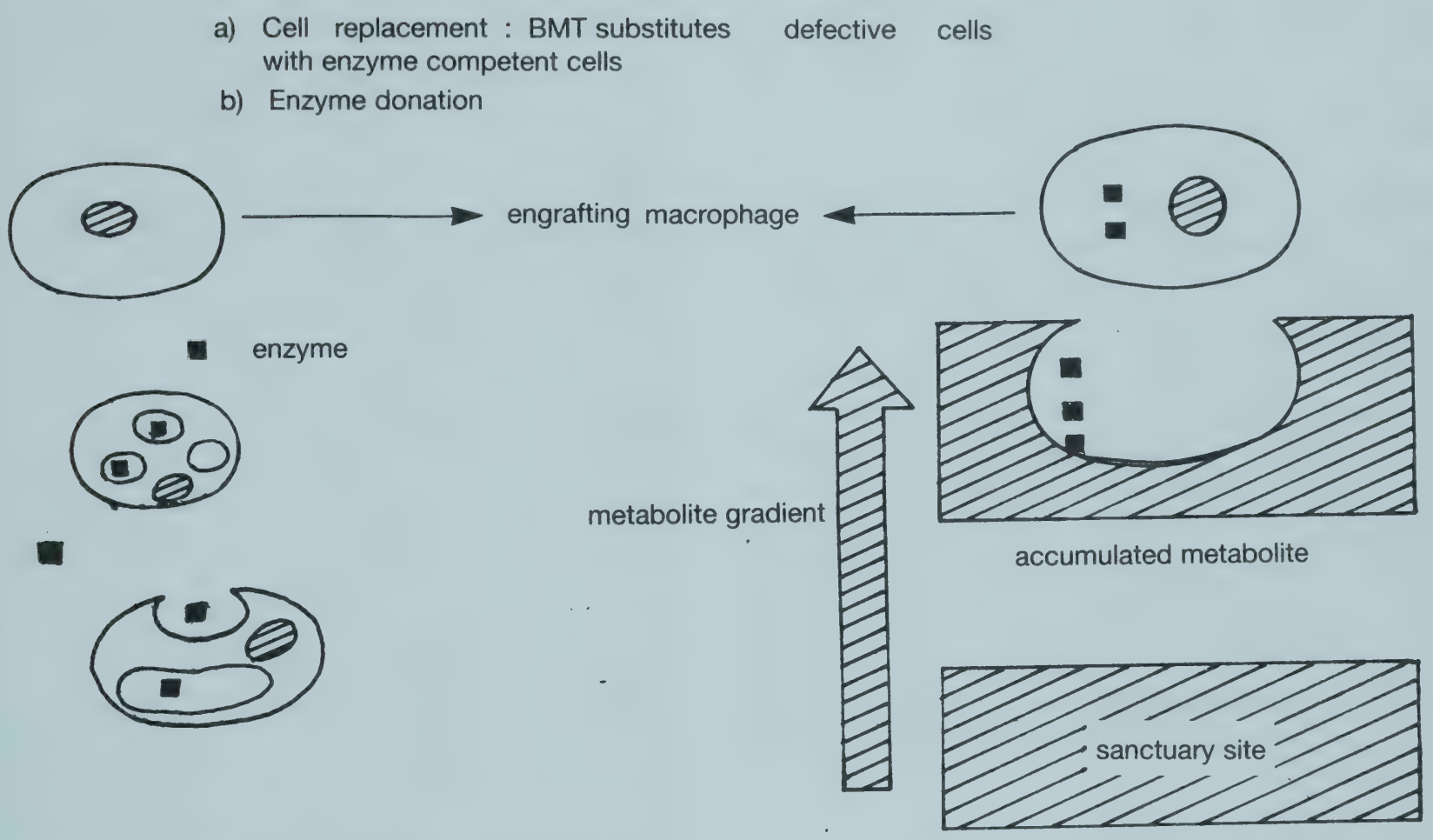

Fig 15.14 Principles involved in the correction of metabolic disorders by bone marrow transplantation

Types of transplants

Syngenic graft: the graft of the donor and the recipient are genetically identical, such as in identical twins.

Allogenic graft: the donor and recipient are genetically different. An HLA-matched allogenic graft is far more easily available than the rare syngenic graft.

Autologous graft: the patient's own marrow is reinfused after irradiation and chemotherapy has eliminated the malignant cells.

Donor selection In order to minimise the risk of graft rejection the recipient should be genotypically identical at the HLA A and B loci and non-reactive in mixed lymphocyte cultures. Though autologous BMT eliminates the risk of rejection, it might still contain viable cancerous cells. These cancerous cells may engraft with the normal cells and can cause a relapse.

Stem cell collection After administration of general anesthesia to the donor, aspiration of marrow tissue from the ribs and iliac crest is performed. 500–1500 ml of blood–bone marrow mixture is collected in a bag containing heparin and tissue culture medium. The donor is given adequate blood replacement after the procedure.

Processing and infusion The aspirated marrow is filtered to remove the particulate material. If the donor marrow is ABO compatible it can

be directly infused intravenously. ABO incompatible marrow is pretreated by centrifugation to reduce the erythrocyte fraction. The leukocyte-rich stem cell preparation is then slowly infused.

Dosage The minimal effective dose has not been conclusively determined but 1×10^8 nucleated marrow cells/kg of recipient weight is considered desirable.

Pretransplant preparative therapy For successful engraftment of donor cells, marrow ablation and immunosuppression of the recipient is essential. If the recipient has not been sensitised by prior transfusions or multiple births, conditioning with cyclophosphamide is sufficient. On the other hand if sensitisation has occurred, both cyclophosphamide and total body irradiation are required.

Risks of BMT Unlike solid organs like kidney, liver, heart and lung which function immediately after transplantation, the bone marrow takes 2–4 weeks for engraftment. During this period, the patient is vulnerable and requires supportive therapy in the form of antibiotics, red cell and platelet transfusions. Interstitial penumonia secondary to pretransplant cytotoxic regimens and opportunistic infections contribute to significant morbidity and mortality. Acute *graft versus host* disease manifesting as a triad of dermatitis, hepatitis and enterocolitis occurs in 60 per cent of patients. Chronic 'graft versus host' disease which mimics autoimmune disease develops weeks to months after transplantation. The steps in bone marrow transplantation are summarised in the information box.

Clinical management of allogenic BMT

Evaluation of recipient prior to transplant

- disease status, stage, prognosis following transplantation, alternate therapies
- cardiac, respiratory, liver and renal functions are assessed
- whether any contraindication exists for BMT

Evaluation of donor

- normal marrow
- compatibility with recipient

Preparation of donor

Immunosuppression: Cyclophosphamide alone in non-sensitised patient. Total body irradiation (TBI) is also performed in sensitised patients. Cyto-reduction requires TBI and busulphan

Marrow collection and transfusion

Collection and sieving of marrow

Problems in immediate posttransplant period

- antibiotics
- platelet and red cell transfusion
- TPN
- fluid and electrolyte management

Problems which occur after a few weeks

- acute GVH
- chronic GVH
- viral infections
- interstitial pneumonitis

GVH = graft versus host disease
TPN = total parenteral nutrition

PERIPHERAL STEM CELL TRANSPLANTATION

Autologous or allogeneic peripheral blood ste cell transplantation is emerging as an alternati to BMT in disorders like lymphomas, leukemi and multiple myeloma.

KEY CONCEPTS

Aplastic anemia

- This is a disorder characterised by bone marrow failure due to a deficiency of the pluripotent stem cell. It may be congenital (Fanconi's anemia with associated skeletal hypoplasia) or acquired (drugs [NSAIDS, chloramphenicol, gold, sulfonyl ureas], radiation, non-A-non-B hepatitis, toxins [benzene, toluene] and pregnancy).
- Symptoms are related to anemia (erythrocyte deficiency), infections (granulocytopenia) and bleeding (thrombocytopenia). Physical examination reveals anemia. Presence of splenomegaly, lymphadenopathy or bone tenderness go against a diagnosis of aplastic anemia.
- The peripheral blood smear shows pancytopenia and a low reticulocyte count. The disorder should be distinguished from other causes of pancytopenia: megaloblastic anemia, PNH, myelophthisic anemia, and myelofibrosis. This is possible with a bone marrow examination. Bone marrow aspiration yields a dry tap while bone marrow biopsy shows extensive hypocellularity.
- Treatment consists of assessing for potential reversible factors; any suspected drug or chemical exposure should be stopped. Any infection should be treated promptly and aggressively. Blood and blood component transfusions (granulocyte, platelet and red cell transfusions) should be used judiciously; bone marrow transplantation must be considered as a therapeutic option early in the course of disease in young patients because transfusions increase the risk of rejection at a future date. Several measures are available to stimulate erythropoiesis; these include androgenic steroids, antithymocyte globulin, hematopoietic growth factors, and glucocorticoids. Immunosuppressants may occasionally be effective but their use is associated with a high complication rate.

15.7 Hematologic malignancies and related diseases

LEUKEMIAS

The leukemias are defined as a heterogeneous group of disorders characterised by malignant monoclonal proliferation of the hematopoietic stem cell with diffused replacement of the bone marrow of the neoplastic cells.

Pathophysiology In acute leukemias, the *blast cells* are blood cell precursors which have been arrested at an immature stage of differentiation. The malignant cells suppress production of normal bone marrow elements causing anemia, infections and bleeding tendencies, features which are characteristic of bone marrow failure. The malignant cells also infiltrate the various organ systems leading to a variable degree of organ system dysfunction.

In contrast, in chronic leukemias the malignant cells differentiate and mature to some

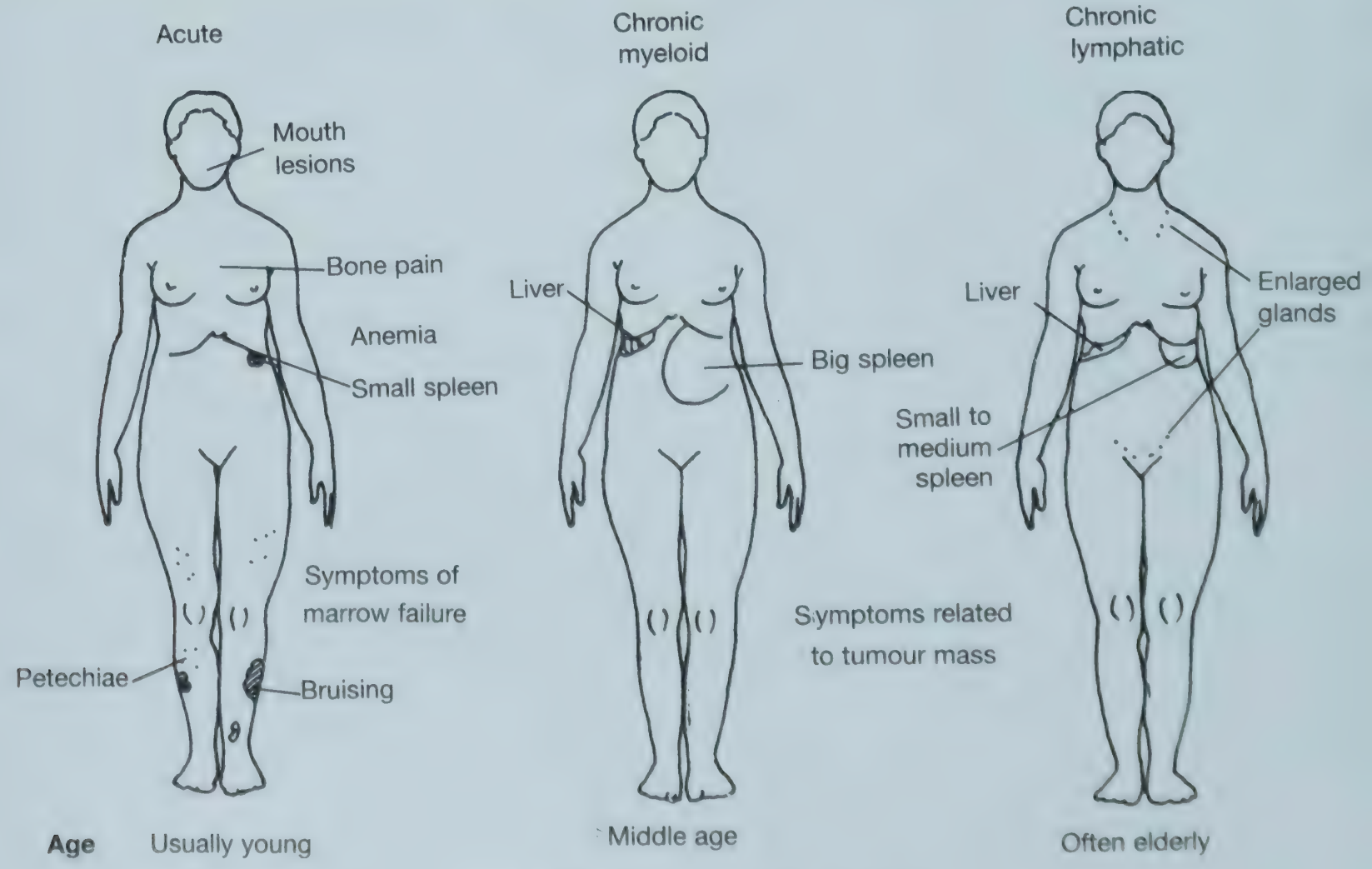

Fig 15.15 Physical signs of the leukemias

degree resulting in vast numbers of mature cells in the peripheral blood. Clinical features are, therefore, due to tumour mass, and marrow failure is a late feature of the disease (Fig 15.15)

Acute Lymphocytic Leukemia (ALL)

ALL can also be classified by immune cell marker studies (Table 15.23). Blast cells which are thymus-derived (T cell lineage) are identified by using monoclonal antibodies to T cell antigens (CD5, CD7). If they are not T cells, they are screened with fluorescein-tagged antimmunoglobulin reagents. If the immunoglobulin is detected on the cell surface, the cell is a mature B lymphocyte. If the immunoglobulin is detected within the cytoplasm (cIg), it is a B lymphocyte precursor.

Only a small group of patients (25%) have T or B cell markers. Other patients (75%) with leukemia, have blast cells which do not react with any of these reagents: these are known as *null cells*. A majority of null cell leukemias express a *common ALL antigen* (CALLA) and the immune-associated (Ia) antigen. In a minority of patients with null cell leukemia the CALLA antigen is not expressed: this is a poor prognostic sign. Another useful cytochemical marker is the *enzyme terminal deoxynucleotidyl transferase* (TDT), a marker for primitive lymphoid cells, that is, null, pre B and T cell leukemic blasts. Since it is an enzyme which is specific for lymphocytes, it helps in identifying leukemic cells in difficult diagnostic situations, for example, to identify whether cells seen in the CSF are lymphoblasts. Staging is not performed in acute leukemias, since the leukemic blast cells have already infiltrated the marrow, lymph nodes, liver and spleen at the time of diagnosis.

Table 15.22 FAB* classification of acute lymphocytic leukemia

Type	*Description*
L1	small cells with scanty cytoplasm
L2	large cells with more cytoplasm
L3	larger cells with abundant vacuolated cytoplasm and cleaved nucleus

* FAB = French-American-British

Incidence Acute lymphocytic leukemia is primarily a disease of children. Only 15 per cent of adult leukemias are of the acute lymphocytic variety.

Clinical features Usually the child is brought to the physician for consultation regarding non-specific symptoms such as failure to recover fully from a viral exanthem or a respiratory infection. Frequently, progressive pallor, fever, bleeding tendencies (due to bone marrow failure), bring the disease to notice.

On initial examination the patient is anemic, febrile with enlarged, non-tender lymph nodes in peripheral accessible areas of the body. Petechial and mucosal bleeds might be present. A third of the patients have bone tenderness due to subperiosteal hemorrhage and periosteal invasion. Mild to moderate splenomegaly is seen in 60–70 per cent of patients but hepatomegaly is much less common. Headache and vomiting are due to raised intracranial tension secondary to meningeal infiltration. Fundus examination reveals hemorrhage with a white deposit in the centre of the bleed, a classic sign of *leukemic retinopathy*. The testes should be palpated for enlargement in order to detect testicular spread.

Investigations Most patients have low hemoglobin levels at the time of diagnosis. The platelet count is also low (less than 100,000/mm^3). Total leukocyte count is more than 30,000/mm^3. A small proportion of patients have counts greater than 50,000/mm^3. Blast cells are seen in the peripheral smear. However, a definitive diagnosis is made only after examination of the bone marrow aspirate. Typically, the marrow is hypercellular and completely flooded with lymphoblasts. A chest X-ray is necessary to rule out a mediastinal mass, a feature common in

Table 15.23 Immunologic classification of ALL

Type of ALL	*Features of abnormal cells*	*Clinical features*
Null cell (65%)	• lack sheep RBC receptors (T cell) and surface Ig (B cell)	• common in children
	• CALLA present	• lymphadenopathy possible
	• Philadelphia chromosome present in 5% of cases	• gum and skin involvement infrequent
	• TDT positive	
T cell (10–12%)	• Lymphoblasts morphologically indistinguishable from null cells;	• occurs in age group10–20 years
	• membrane receptors for sheep RBCs present	• mediastinal lymphadenopathy and CNS inflitration
	• T cell antigens present	
	• TDT positive	
B cell (< 2%)	• large blasts with vacuolated deeply basophilic cytoplasm	• poor long-term prognosis
	• t (8,14) chromosomal abnormality	
	• surface Ig present	
	• TDT negative	
pre-B cell 10–12%	• negative for T cell antigens B cell antigens, CALLA antigen TDT ±	• commited to B cell with cytoplasm Ig

CALLA = common acute lymphoblastic leukemia antigen; TDT = terminal deoxynucleotidyl transferase
Ig = immunoglobulin

patients with T cell leukemias. X-ray of the long bones (taken when the patient presents with severe pain in the bone) may reveal subepiphyseal bone resorption ('leukemic zones'), cortical defects or altered medullary trabeculae. The CSF is routinely examined for blast cells, the presence of which is of great prognostic significance.

Blood urea, creatinine, serum potassium and uric acid levels are determined prior to starting therapy. Tumour lysis will cause hyperkalemia and hyperuricemia and monitoring levels of these analytes is helpful in controlling the adverse effects of excess tumour cell lysis.

Differential diagnosis Bone marrow failure associated with aplastic anemia and myelofibrosis needs to be distinguished from ALL. A bone marrow study usually resolves the diagnosis. Neuroblastoma, retinoblastoma and Ewing's sarcoma also infiltrate the bone marrow; these disorders usually present with a clinically obvious primary focus. Infectious mononucleosis is often confused with ALL but a marrow populated with normal cells is a feature of this infection.

Treatment It comprises of several phases: induction therapy, prophylaxis, continuation and treatment of relapse. Supportive measures are needed throughout :

1. psychosocial counselling,
2. prevention and control of bleeding,
3. avoidance and control of infection,
4. allopurinol to limit hyperuricemia (and possible urate nephropathy),
5. red cell transfusion for correction of anemia,
6. fresh platelet transfusion for severe thrombocytopenia,
7. antibiotics for serious infections (granulocyte transfusion), and
8. avoidance of live vaccines.

Induction therapy: The aim of this phase of treatment is to completely eradicate the leukemic blast cell from the bone marrow, that is, to induce 'remission'. Vincristine and prednisolone (often with L-asparaginase and doxorubicin) are used for induction. The *consolidation phase* uses the drugs cyclophosphamide and L-asparaginase.

Prophylaxis: The CNS is a *sanctuary site* for the leukemic blast cells, that is, drugs administered systemically fail to reach therapeutic concentrations within the CSF. Therefore, drugs are directly introduced into the CSF. Standard risk patients need bimonthly intrathecal administration of drugs. If CNS spread is detected at the time of diagnosis, craniospinal irradiation along with intrathecal drug administration is necessary.

Systemic continuation treatment: Once remission has been successfully induced, maintenance therapy is continued for another 2–2.5 years. Methotrexate and 6-mercaptopurine are used in this phase. Periodically drugs used for induction therapy are repeated: this is a form of reinforcement therapy.

The response of patients with L3 morphology and surface immunoglobulins has been poor. They are being given the benefit of an early bone marrow transplant along with treatment regimens designed for B cell lymphomas. Patients with T cell leukemia do respond to the regimens administered to standard risk ALL. However, most patients will relapse within two years. More intense multiagent chemotherapy has been used to induce long term remission.

Relapse: Reappearance of blasts is usually detected in the blood, marrow, testes or CNS. This indicates that the patient is having a relapse. CNS leukemia manifests as raised intracranial tension, that is, headache, vomiting, papilledema, progressive lethargy and convulsions. In such patients the CSF pressure is elevated and fluid analysis reveals pleocytosis (leukemic blasts).

If CNS relapse occurs when the patient is in hematological remission, intrathecal methotrexate is given once a week for 4–6 weeks until the cells disappear from the CSF. Craniospinal irradiation should also be given. Systemic chemotherapy is intensified. Testicular relapse produces a painless asymptomatic enlargement of the testes. Diagnosis is confirmed by a testicular biopsy. The retroperitoneal lymph nodes drain the gonads; hence seeding of the retroperitoneal lymph nodes is possible with testicular relapse. Treatment, therefore, includes irradiation of the gonads (2000 rads) and intensive systemic chemotherapy. Preventive CNS therapy is also repeated.

Bone marrow aspirate studies are performed at regular intervals. If a bone marrow relapse occurs, intensive chemotherapy with cytosine arabinoside and epipodophyllotoxin (VM26) will achieve cure in a significant number of patients. Bone marrow transplantation should be considered.

Prognosis Favourable prognostic factors are

1. age between 2 and 10 years,
2. no CNS involvement at the time of diagnosis,
3. absence of mediastinal involvement,
4. total leukocyte count $<100{,}000/mm^3$,
5. blast cells which do not have T or B cell functions, and
6. CALLA positive, null cell leukemia.

Patients who fulfil the above criteria are said to have a *standard risk*. CALLA positive null cell

ALL with standard risk factors have the most favourable prognosis. Ninety-five per cent of patients achieve prolonged remission and cure. In India, intercurrent infections (while the patient is under treatment) account for the majority of deaths. T cell leukemia is curable in 50 per cent of patients in optimal conditions. B cell leukemia is rarely cured with existing regimens.

Acute Myeloid Leukemia (AML)

Acute myeloid leukemia is more common in older children and younger adults. Its incidence is equal in both sexes.

Predisposing factors AML occurs frequently in syndromes characterised by chromosomal leakages e.g. Fanconi syndrome, Bloom syndrome and ataxia telangiectasia. Besides, it is one the most common tumours occurring secondary to cancer chemotherapy.

Pathology AML is classified by morphological features into seven subtypes (M1–M7) according to the French-American-British group. The degree of similarity of the leukemia blast cell to the normal precursor cell in the marrow helps in classifying the cell type (Tables 15.24 and 15.25). The M3 type is characterised by the fusion of the retinoic acid α receptor on chromosome 17 to the 'PML' locus on chromosome 15.

Clinical features Fever, pallor, lassitude, recurrent surface bleeding tendencies and bone pain occur over a period of 6–8 weeks. It is usually not possible to clinically differentiate between ALL and AML. Gum infiltration and a localised intraorbital tumour mass (***chloroma***) leading to proptosis are two of the findings relatively specific to AML. Two-thirds of all patients with AML have hepatosplenomegaly. Twenty per cent have marked lymphadenopathy. The above clinical features are common to all types of AML. In addition promyelocytic leukemia (M3) is characterised by a predisposition to disseminated intravascular coagulation.

Investigations The hemoglobin level, platelet and leukocyte counts are similar to that of patients with ALL. A baseline coagulation profile is necessary in acute promyelocytic leukemia. A bone marrow aspirate study confirms the diagnosis. Since characteristic karyotypic abnormalities occur in AML, chromosomal analysis of the marrow is indicated. Occasional AML occurs after a prolonged period of progressive marrow failure.

Table 15.24 Laboratory distinction between AML and ALL

	AML	*ALL*
1. Morphology of leukemic blasts	Granules in cytoplasm; Auer rods* may be present (10–20%, especially M3) Multiple nucleoli	Agranular, basophilic cytoplasm Regular, folded nucleus with one prominent nucleolus
	FAB (see Table 15.25) subclassification, M1–M7	FAB subclassification, L1–L3
2. Histochemistry	Myeloperoxidase positive	Myeloperoxidase negative; PAS positive
3. Cytoplasmic markers	–	Terminal deoxynucleotidyl transferase (Tdt) positive
4. Surface markers (% of cases)	–	B cell markers (5%) T cell makers (15–20%) CALLA** (50–65% cases)

* Auer rods are a linear coalescence of cytoplasmic granules which stain pink with Wright's stain.
**CALLA = Common acute lymphoblastic leukemia antigen

Table 15.25 FAB classification of acute myeloblastic (myelocytic) leukemias (AML)

FAB Class	% of AML	Morphology	Histochemistry
M1 Acute myelocytic leukemia without differentiation	20	Myeloblasts predominate; distinct nucleoli; few granules or Auer rods	Myeloperoxidase +
M2 Acute myelocytic leukemia with differentiation	30	Myeloblasts and promyelocytes predominate; Auer rods may be present	Myeloperoxidase +++
M3 Acute promyelocytic leukemia	5	Hypergranular promyelocytes; often with many Auer rods per cell; may have reniform or bilobed nuclei	Myeloperoxidase +++
M4 Acute myelomonocytic leukemia	30	Myelocytic and monocytic differentiation evident; myeloid elements resemble M2; peripheral blood monocytosis	Myeloperoxidase ++ *Non-specific esterase +
M5 Acute monocytic leukemia	10	Promonocytes or undifferentiated blasts	*Non-specific esterase++
M6 Acute erythroleukemia	5	Bizarre, multinucleated, megaloblastoid erythroblasts predominate; myeloblasts also present	Myeloperoxidase + (Myeloblasts), PAS + (Erythroblasts)
M7 Acute megakaryocytic leukemia	5	Pleomorphic undifferentiated blasts; react with antiplatelet antibodies; myelofibrosis or increased bone marrow reticulin	Platelet peroxidase + by electron microscopy

* Reaction inhibited by sodium fluoride; FAB = French-American-British Group

The proportion of blast cells might be so small that it is difficult to diagnose leukemia. In such patients demonstration of an abnormal karyotype helps in restoring the diagnostic uncertainty. Where histological classification is not clear monoclonal antibodies are currently being used for typing the leukemia.

Treatment Myeloid blast cells closely resemble normal stem cells. The cytotoxic regimens used in treating AML will inevitably lead to marrow aplasia. Hence stringent aseptic precautions are essential in the management of these patients. Drugs used are continuous intravenous cytosine arabinoside for seven days and i.v. daunorubicin for three days. Maintenance chemotherapy is given for two years by rotating multiple chemotherapeutic drugs. CNS prophylaxis is similar to that given to patients with ALL. When the patient goes into remission, allogenic bone marrow transplantation is advocated. All-trans retinoic acid corrects the basic defect in M3 and induces remission.

Prognosis The cure rate for AML is much lower than that of ALL but has improved recently. Thirty to forty per cent of patients can achieve cure under optimal conditions. AML secondary to myelodysplastic syndromes and resulting from cancer chemotherapy show a much poorer response to treatment than patients with primary AML.

Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia is a chronic lymphoproliferative disorder characterised by the malignant transformation of lymphoid precursors, most often of the B cell lineage. The long-lived, non-functional B lymphocytes infiltrate the lymph nodes, blood, bone marrow and other tissues.

Pathophysiology Though lymphocytes in CLL are long-lived, they are *immunoincompetent,* that is, they are not able to differentiate into antibody-secreting plasma cells. They possess

surface immunoglobulins specific for mature B lymphocytes (CD19, CD20), but do not contain TdT or express CD10, a B cell precursor antigen, thus differing from lymphoblasts. Fifty per cent of patients have abnormal karyotypic features, of which trisomy 12 is the commonest.

Incidence Chronic lymphocytic leukemia is a disease of the elderly (40–70 years of age). B cell CLL accounts for 95 per cent of patients with chronic lymphocytic leukemia. T cell CLL occurs only in 5 per cent and is more prevalent in Asians; it is associated with a poor prognosis and prominent skin involvement.

Clinical features Chronic lymphocytic leukemia has an insidious onset. It is diagnosed by examination of a routine peripheral smear in an otherwise healthy person. Lethargy, fatigue, fever and weight loss are the most common presenting features. Generalised painless lymphadenopathy (75%) and moderate splenomegaly (50%) are prominent findings on examination.

Course The disease follows an indolent course. After a variable period ranging from a few months to years, symptoms of bone marrow failure such as progressive anemia, bleeding tendencies and infections (secondary to hypogammaglobulinemia) set in. In rare cases the disorder can transform into a more aggressive leukemia (*prolymphocytic leukemia*) or into an aggressive diffuse histiocytic lymphoma (*Richter syndrome*).

Investigations The peripheral blood film reveals lymphocytosis of greater than 15×10^9/L. Normocytic, normochromic anemia with normal platelet counts are observed early in the disease. A Coomb's positive hemolytic anemia may develop subsequently. Lymphocytic infiltration of the bone marrow (>40% of cells are lymphocytes) is diagnostic of the disease. The staging of chronic lymphocytic leukemia is shown in Table 15.26.

Treatment In the early stages of the disease, no treatment is required. Alkylating agents such as chlorambucil and cyclophosphamide given for 4–8 weeks induce partial remission in two-thirds of the patients. Steroids are used for their antitumour effects, for the supression of immune hemolytic anemia, for alleviation of thrombocytopenia and hypercalcemia. A common regimen consists of chlorambucil (0.6–1 mg/kg) combined with 4 days of prednisone every 21 days. Supportive care include the use of antibiotics and gamma-globulins for infections. Blood transfusions help to correct anemia. Fludarabine is a new experimental drug for use in refractory cases. The indications for two other new drugs, deoxycoformycin and 2-chlorodeoxyadenosine, are under investigation.

Prognosis The overall median survival of CLL patients is 4–6 years. Survival depends on the stage of the disease (Table 15.26). Transformation to an acute leukemia (as is seen in CML) is very rare. It is important to reassure these patients as they can often lead a normal life despite the frightening diagnosis of leukemia.

Hairy Cell Leukemia

It is a chronic lymphoproliferative disorder in older men with a peculiar morphology of the leukemic cells which are fine. In addition hair-like projections can be seen under an ordinary microscope.

The malignant cell in hairy cell leukemia expresses surface markers of T cells, B cells and monocytes. Molecular analysis, however, establishes the B cell lineage of these cells. Another distinctive histochemical feature is the presence of an enzyme *tartrate-resistant acid phosphatase* (TRAP).

Clinical features Massive splenomegaly, moderate hepatomegaly and peripheral pancytopenia with a fibrotic marrow are the most important manifestations of the disease.

Table 15.26 Staging classification of CLL

Stage	Description	Median survival
A	Lymphocytosis >10,000 mm^3/L; no anemia or thrombocytopenia; <3 areas of lymphoid enlargement	10 years
B	>3 areas of lymphoid enlargement No anemia or thrombocytopenia	5 years
C	Anemia or/and thrombocytopenia regardless of the number of areas of lymphoid enlargement	2 years

Clinical enlargment of spleen, liver, cervical, axillary and inguinal lymph nodes constitute five different areas of involvement. Each of these five anatomic regions are considered as lymphoid regions for the purpose of this classification.

The diagnosis is based on the characteristic morphologic appearance.

Treatment Alpha interferon is of benefit in the management of hairy cell leukemia. Deoxycoformycin and 2-chlorodeoxyadenosine are also extremely effective. Splenectomy is now rarely performed.

LYMPHOMAS

Lymphomas are self-perpetuating malignant proliferation of the lymphoreticular cell system. Lymphomas are classified into Hodgkin's lymphoma and non-Hodgkin's lymphoma. Lymphomas may also be classified based on their cell of origin using immunologic and molecular biologic techniques (Table 15.27).

Hodgkin's Lymphoma

Hodgkin's disease (HD) is a lymphoreticular malignancy characterised by the presence of distinctive neoplastic giant cells called the *Reed-Sternberg cells* (RS cells) which are interspersed with a variable polycellular inflammatory infiltrate.

Pathology The Reed-Sternberg (RS) cell, varies between 15–45 μm in size. It has abundant eosinophilic cytoplasm. Its distinguishing feature is the presence of the multilobate, *mirror image nucleus*, with large round prominent nucleoli surrounded by a clear zone. This gives it a peculiar *owl-eyed* appearance. Though the RS cell is pathognomonic of Hodgkin's disease, it is also found in a variety of other disorders like infectious mononucleosis, mycosis, fungoides

Table 15.27 Technique used in the diagnosis of lymphoid neoplasms

Cell type	Technique		
	Immunologic[1]	Molecular[2]	Histochemical
T cells	Monoclonal antibodies	T cell receptor gene rearrangement	–
B cells	Cell surface immunoglobulins[3] Monoclonal antibodies	Immunoglobulin gene rearrangements	–
Histiocytes	Monoclonal antibodies	–	Non-specific esterases

1 Immunologic techniques usually employ indirect immuofluorescence on frozen tissue sections or flow cytometry on cell suspensions.
2 Molecular biologic techniques depend on demonstration of T-cell receptor or immunoglobulin gene rearrangements in the DNA extracted from tumour cells.
3 Clonal (neoplastic) proliferation of B cells is indicated by the presence of an immunoglobulin of a single light chain type. Cytoplasmic immunoglobulin, in the absence of surface immunoglobulin, is seen in pre-B cells.

and non-Hodgkin's lymphoma. Four histological subtypes have been described in Hodgkin's disease. These are lymphocyte predo-minant HD, mixed cellularity HD, lymphocyte depleted HD, and nodular sclerosis HD.

Lymphocyte predominant Hodgkin's disease
This subgroup is characterised by a dense lymphocytic infiltrate admixed with benign histocytes. Neutrophils, eosinophils and plasma cells are absent. A few RS cells can be identified. There is no fibrosis or necrosis.

Mixed cellularity Hodgkin's disease
This subtype has fewer lymphocytes when compared to the lymphocyte predominant variety. However, eosinophils, plasma cells and benign histiocytes are plentiful. Typical RS cells are also more abundantly present. Small areas of fibrosis and necrosis are commonly seen.

Lymphocyte depletion Hodgkin's disease
This disease is, as the name indicates, characterised by a paucity of lymphocytes. However RS cells and its variants are plentiful. This subgroup of Hodgkin's disease is further divided into two morphological forms:
1. Diffuse fibrosis varient where the node is replaced by a proteinaceous, fibrillar material. Lymphocytes, typical and atypical RS cells are few and scattered with the fibrillar material.
2. The reticular variant is more cellular. It is composed of large pleomorphic, anaplastic cells, which resemble RS cells but which are not typical.

Nodular sclerosis Hodgkin's disease
This differs from the other subtypes by the presence of two characteristic features.
1. The 'lacunar' cell is a large cell with abundant cytoplasm and a single nucleus within which are multiple nucleoli. The cytoplasm of the cell is peculiar in that it appears retracted from the surrounding cells, giving rise to the appearance of a cell lying within a clear space or 'lacunae'.
2. The other peculiar feature is the presence of collagen bands which divide the lymphoid tissue into nodules.

Incidence The disease is more common in males than in females, with the exception of nodular sclerosis which is the only variety of Hodgkin's lymphoma more frequently found in women. There is a bimodal incidence, with the first peak occurring between 15 and 35 years and the second after the age of 50 years.

Clinical features The commonest presenting feature of Hodgkin's lymphoma is a painless progressive asymmetrical lymphadenopathy. Occasionally symptoms arise due to compression of adjacent structures by the lymphomatous masses. Dysphagia due to esophageal compression, superior vena caval syndrome secondary to impingement on the superior vena cavae, or cough due to pressure on the tracheobronchial tree are some presenting features of Hodgkin's disease. The nodes are non-tender, matted and rubbery and usually involve the cervical, axillary and inguinal regions. Splenomegaly is encountered in 50–70 per cent of cases.

Non-specific systemic symptoms like pruritus, fever, weakness and weight loss (of greater than 10 per cent over the preceding six months), and drenching night sweats, are initial complaints in a minority of patients. Such patients are diagnostic dilemmas, since enlarged lymph nodes are clinically undetectable. Hence, these patients may often require a CT scan or laparotomy to establish the diagnosis of Hodgkin's disease. The various stages are given in Table 15.28 and Fig 15.16.

Investigations An abnormal peripheral smear is observed in 30 per cent of patients at the time of diagnosis of Hodgkin's disease. Normocytic, normochromic anemia is the commonest feature. Autoimmune hemolytic anemia is also frequently present. Total leukocyte counts are

Table 15.28 Clinical stages of Hodgkin's and non-Hodgkin's lymphomas (Ann Arbor classification)

Stage	*Distribution of disease*
I	Involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or site (I_E).
II	Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or with involvement of limited contiguous extralymphatic organ or tissue (II_E).
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (III_S) and/or limited contiguous extralymphatic organ or site (III_E,III_{ES})
IV	Multiple or disseminated foci of involvement of one or more extralymphatic organs or tissues with or without lymphatic involvement

All stages are further divided on the basis of the absence (A) or presence (B) of the following systemic symptoms: significant fever, night sweats, and/or unexplained weight loss of greater than 10% of normal body weight.

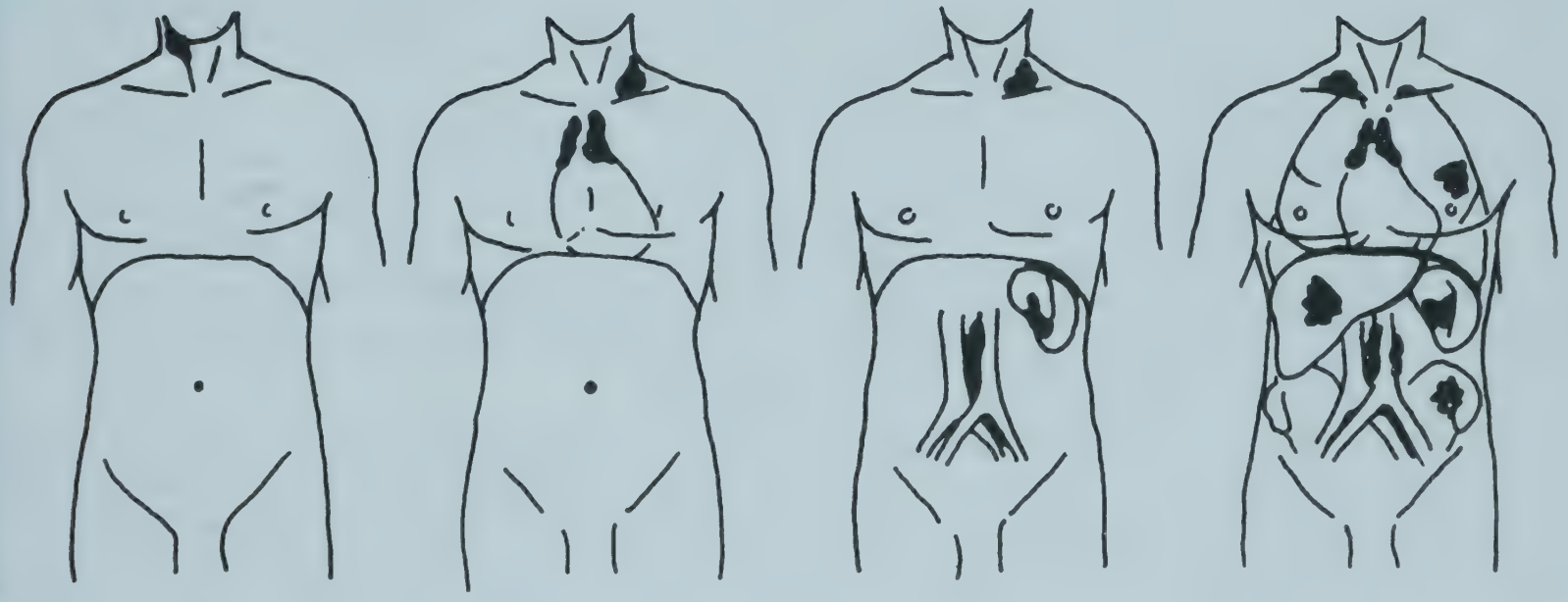

Fig 15.16 Malignant lymphoma: examples of stages I through IV

increased with significant granulocytosis and monocytosis. Eosinophil counts are elevated in 10–20 per cent of patients.

A platelet count exceeding 400,000/mm^3 is also occasionally encountered. The ESR is often elevated.

There is a delayed cutaneous hypersensitivity reaction due to impaired cell mediated immunity. Hence, patients have an increased susceptibility to cryptococcus, tuberculosis and herpes zoster infections. Serum electrophoretic studies are normal early in the disease. Later, mild hypoalbuminemia and hyperglobulinemia might be noted. Occasionally, serum calcium and uric acid levels are elevated. A lymph node biopsy is necessary to confirm the diagnosis. *Staging* is done in order to establish the extent of the disease. An X-ray of the chest is necessary to rule out mediastinal involvement.

Lymphangiography, ultrasound scan and CT of the abdomen will reveal clinically silent disease within the abdomen. A CT scan alone, however, cannot replace a lymphangiogram since it is not sensitive enough to pick up minimal node involvement.

Laparotomy, coupled with histopathological examination of tissue samples from the nodes, spleen and liver is the most informative procedure. It is particularly useful, when the lymphangiogram is non-contributory.

Treatment (Table 15.29) Localised Hodgkin's disease (Stages I and II) is treated with radiotherapy. 4000–4500 rads is administered to the involved areas over a period of 4–5 weeks. Patients with III B (i.e., with systemic symptoms) require combination chemotherapy with radiotherapy to prevent early relapse. Some of these patients are able to live disease-free for at least 5 years. Stage III A is treated with only radiotherapy where facilities are available. Most institutions, however, manage such patients with multiagent chemotherapy. Patients with Stage III B and IV are best treated with combination chemotherapy. Drugs useful in the management of Hodgkin's disease are

MOPP mustine, oncovine, procarbazine and prednisolone

MVPP mustine, vinblastine, procarbazine, prednisolone

ABVD adriamycin, bleomycin, vinblastine, dacarbazine

A combination of antitumour drugs with different modes of action given concurrently and repeatedly over a six month period can induce remission. Radiation is employed in Stage II and IV disease to help reduce the size of the tumour.

Table 15.29 Treatment of Hodgkin's disease

Stage of Hodgkin's disease	*Initial therapy*
I	Radiation
II	Radiation
III A	Radiation
III B	Combination chemotherapy
IV	Combination chemotherapy

Course Hodgkin's disease in young adult follows a predictable course. The disease spreads by the involvement of adjacent lymphatic tissue and is potentially curable. In the elderly it follows a more aggressive course and is often multicentric at the time of diagnosis.

The presence of constitutional symptoms is an unfavourable prognostic factor. Women fare consistently better than men irrespective of the stage of the disease. Pregnancy has no adverse effect on the outcome of the disease.

Prognosis Lymphocyte predominance type of histology offers the best prognosis with a five year survival rate of 50–60 per cent. This is followed closely by nodular sclerosis Hodgkin's disease. Lymphocyte depleted Hodgkin's disease is an aggressive tumour and offers a worse prognosis with a five-year survival rate of less than 10 per cent.

Non-Hodgkin's Lymphomas

Non-Hodgkin's lymphomas form a heterogeneous group of lymphoreticular malignancies with varying clinical presentation. Although it resembles Hodgkin's disease in that it arises from the lymphoid tissue, it lacks the characteristic Reed-Sternberg cell. Immunologic studies indicate that the majority of non-Hodgkin's lymphoma are of B cell lineage. CLL and well differentiated lymphocytic lymphoma have such striking similarities with NHL that they may in fact be closely-related neoplasms of B lymphocytes. Even the histiocytic lymphoma appears to be of B cell origin.

Classification No single universally accepted system of classification of non-Hodgkin's lymphoma exists. The National Cancer Institute of USA offers a working formulation which is based on the biologic behaviour of the tumour and is now being used widely. It divides tumours into

Low grade: wherein the untreated population, median survival is five to seven years;

Intermediate grade: where survival is shortened to two to three years;

High grade: which follows a fulminant course and death occurs within two years.

Table 15.30 A working formulation of non-Hodgkin's lymphomas (National Cancer Institute, USA)

Low grade
A. Small lymphocytic
B. Follicular, predominantly small cleaved cell
C. Follicular, mixed small cleaved and large cell
Intermediate grade
D. Follicular, predominantly large cell
E. Diffuse, small cleaved cell
F. Diffuse, mixed small and large cell
G. Diffuse, large cell
High grade
H. Large cell, immunoblastic
I. Lymphoblastic
J. Small non-cleaved cell
Miscellaneous

Clinical features The manifestations of the different types of non-Hodgkin's lymphoma are diverse. Therefore only a few types are described here. Clinical differences from Hodgkin's disease are depicted in Fig 15.17.

Small cell lymphocytic lymphoma

This disorder is seen in patients over the age of 50 years. Men are affected twice as often as women. There is progressive, painless, symmetrical, generalised lymphadenopathy. The nodes are discrete and not adherent to the underlying tissues. Lymphoid tumour masses are present in the nasopharynx, oropharynx and the tonsillar regions. In 10 per cent of patients the gastrointestinal system is also involved. Splenomegaly is present in 20 per cent of cases. Tissue diagnosis obtained by biopsy of affected lymph nodes reveals small unstimulated lymphocytes with dark round nuclei and scanty cytoplasm. The bone marrow is filled with these cells. In 40 per cent of patients, the neoplastic cells are also seen in the peripheral blood smear which makes this disease difficult to differentiate from chronic lymphocytic leukemia.

Follicular, small 'cleaved' cell lymphoma

This lymphoma is more common in adults, males and females being equally affected. Painless generalised lymphadenopathy, which waxes and wanes in size is the presenting feature. Other manifestations are similar to that of the small lymphocytic lymphoma. Histopathologically, this subtype is characterised by small normal-looking lymphocytes with a clear nuclear contour. Overall survival is good since the tumour follows an indolent course. Spontaneous regressions are common in this type of lymphoma.

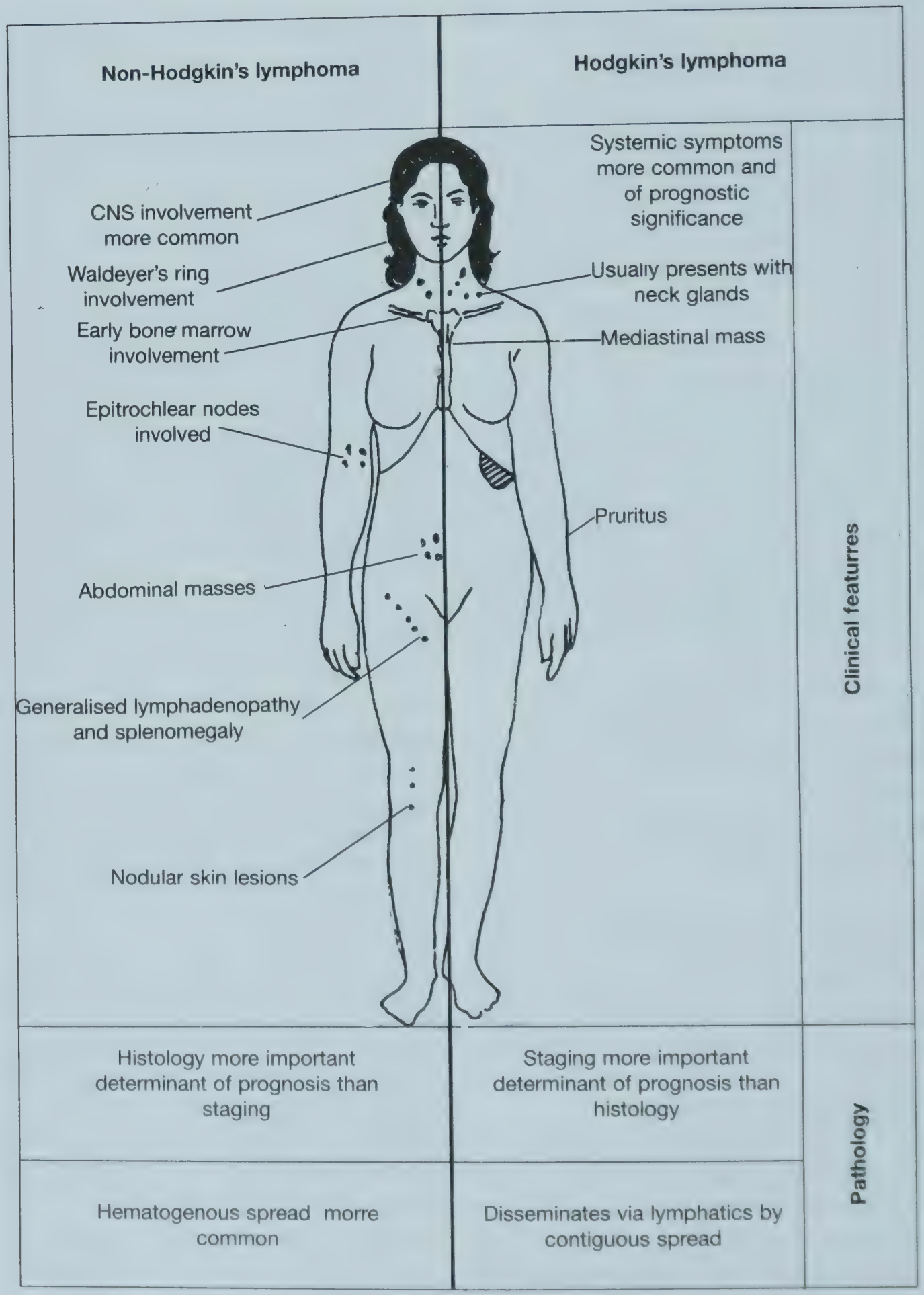

Fig 15.17 Comparison of Hodgkin's and non-Hodgkin's lymphoma

Diffuse large cell lymphoma

This occurs in all age groups, with an equal incidence in men and women. The initial manifestations of the disease include painless, matted asymmetrical, regional lymph node enlargement. Extranodal tumour masses are encountered in the oropharynx, nasopharynx, tonsils, skin and bone. Mediastinal and retroperitoneal tumours produce symptoms due to pressure effects on nearby organs.

The tumour cells have a *plasmacytoid* appearance. This subtype follows an aggressive course, but Stages I and II of the disease are amenable to treatment with the possibility of a complete remission.

Diffuse lymphoblastic lymphoma

Children and young adults are commonly affected. The incidence in males is twice that in females. The patients present with life-threatening problems like airway obstruction, compression of the superior vena cavae, massive pleural and pericardial effusions secondary to large mediastinal tumours. The disease is rapidly progressive. Early dissemination to the bone marrow, blood and meninges is frequent. The cellular morphology is similar to acute lymphoblastic leukemia. Immunobiologic observations have established the T cell lineage of these tumours. The disease follows an aggressive course if left untreated. Recent treatment protocols, however, have improved the prognosis of these tumours.

Small 'non-cleaved' cell lymphoma

Burkitt's lymphoma falls within this category. This lymphoma occurs in children below 14 years of age in certain regions of tropical Africa. This tumour characteristically involves the jaws, facial bones and the intraabdominal viscera. Leukemic spillover into the blood is rare. Translocation of the protooncogene 'c-myc' from its normal position on the long arm of chromosome 8 to the heavy chain locus on the long arm of chromosome 14 has been identified as a possible cytogenetic mechanism for this disease. The neoplastic cells are 10–25 μm in diameter with a '*pyroninophilic*'[1] cytoplasm. They fill the tumour with a 'sea of strikingly monotonous cells'. Macrophages which lie interspersed among the latter are often surrounded by clear spaces ('*starry sky appearance*'). The etiology of this variety of B cell lymphoma has been postulated to be the Epstein-Barr virus. Burkitt's tumour is highly responsive to chemotherapy.

Staging Lymph node biopsy confirms the type of NHL affecting the patient. The staging procedures are similar to that of Hodgkin's disease. After a tissue diagnosis is obtained, bone marrow aspiration studies, CSF analysis, CT scan, bipedal lymphangiogram and ultrasonograms are performed to study the extent of the disease. Since most patients are in Stage III, or IV at the time of diagnosis, a staging laparotomy is not usually required. Serum LDH levels have been used as prognostic markers; elevated levels indicate extensive and aggressive disease.

Treatment For *low grade tumours* following an indolent course, the therapeutic approach is essentially palliative. Chlorambucil and cyclophosphamide, vincristine and prednisolone are being used in Stages III and IV with the intent of reduction in tumour size, and resolution of symptoms. *Intermediate* and *high grade tumours* are treated with combination chemotherapy for a period of six months or more. Though most patients appear to enter a phase of complete remission, 20 per cent will show evidence of persistent tumour when reexamined carefully. Hence *restaging* is an essential step which is taken to prevent premature cessation of therapy. CNS prophylaxis is advocated in high grade lymphomas. Radiotherapy of 4000 rads over 4–5 weeks is used to treat *localised lymphomatous*

[1] Pyroninophilic is the ability to bind dye pyronine. Such cells stain deep red due to a rich content of cytoplasmic RNA.

tumours (Stages I and II). The efficacy of bone marrow transplantation is currently being evaluated in the treatment of non-Hodgkin's lymphoma. The median survival is 6–8 years in patients with indolent lymphomas.

MYELOPROLIFERATIVE DISORDERS

This group of disorders arises from the malignant clonal proliferation of the pluripotent myeloid stem cell (Fig 15.18 and Table 15.31).

The type of disorder depends on the dominance of a particular ALL clone. Thus, if the granulocytes dominate, the resulting disorder is chronic myeloid leukemia. If erythroid precusors are excessive the diagnosis is polycythemia rubra vera (PRV). Dominance of megakaryocytes is manifested as essential thrombocythemia.

Although the individual diseases have distinctive clinical features, interconversions between these groups is possible during the course of the disease. For instance, patients with PRV may convert to myeloid metaplasia. Subsequently the marrow undergoes fibrosis resulting in myelofibrosis.

Chronic Myeloid Leukemia (CML)

Incidence It occurs between the ages of 25 and 60 years. There is a higher incidence in men.

Pathophysiology The majority of patients with CML have a distinctive chromosomal anomaly which can be demonstrated in the erythrocytic granulocytic and platelet precursors and is known as the *Philadelphia chromosome*. It results from the reciprocal translocation of the long arm of chromosome 9 to the long arm of chromosome 22. As a consequence of this rearrangement, there are abnormalities in the function of growth factors or their receptors leading to a malignant transformation of the

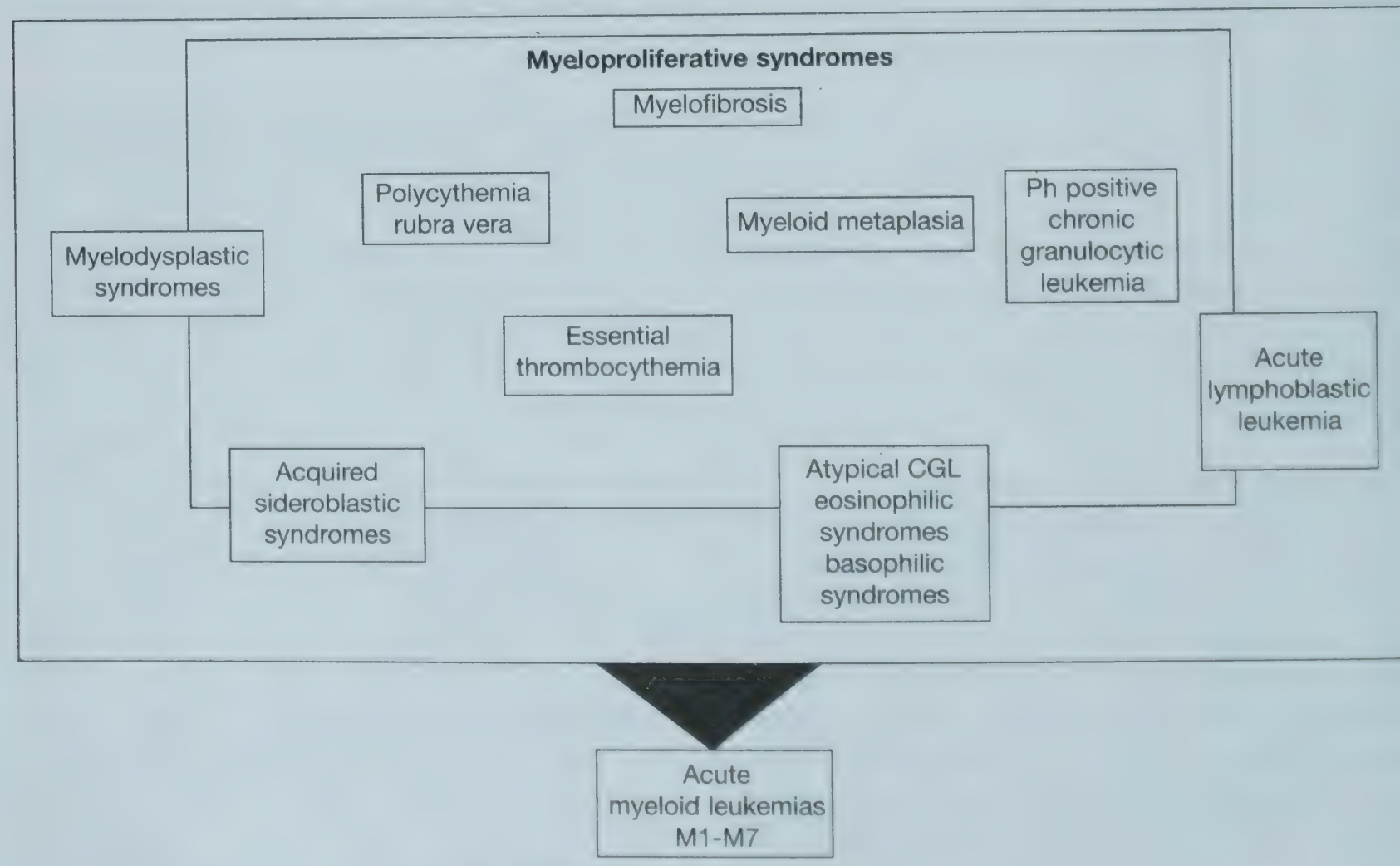

Fig 15.18 The myeloproliferative spectrum

Table 15.31 Classification of myeloproliferative disorders

FAB classification	*Cytogenetics*	*Morphology*
Polycythemia rubra vera (PRV)	$t8^{+}$, $20q^{-}$	Hypercellular pan-myelopathy
Chronic myeloid leukemia (CML)	t (9,22)	All marrow elements are increased
Essential thrombocythemia	–	Platelet count exceeds 1000 X 10^9/L; moderate increase in all elements
Myelofibrosis	–	Leukoerythroblastosis, myelofibrosis and extramedullary hematopoiesis

affected stem cell. This results in an abnormal uncontrolled proliferation of stem cells within the marrow with spillover of vast numbers of mature cells into the peripheral blood.

Clinical features The onset of disease is insidious, with lassitude, fatiguability, weight loss, pallor and anorexia occurring as the initial clinical manifestations of the disease. Pallor, bleeding and infections are suggestive of bone marrow failure. Massive splenomegaly is another important characteristic of this disease. Increased cell turnover causes hyperuricemia and occasionally clinical gout.

Patients remain stable for 2–3 years after which 50 per cent enter an accelerated phase characterised by progressive marrow failure, increasing cytogenetic abnormalities and eventually transformation into acute leukemia: this is known as the *blast crisis*. During this accelerated phase, the response to treatment is poor and patients rapidly succumb to the illness.

Investigations Total leukocyte count typically exceeds 100,000/mm^3. Mature neutrophils, metamyelocytes, basophils and eosinophils predominate in the peripheral blood. Myeloblasts can also be demonstrated in the peripheral smear. The platelet count is elevated. The granulocytes lack alkaline phosphatase, a feature which differentiates CML from leukemoid reactions.[1] Identification of the Philadelphia chromosome is pathognomonic of the condition.

Management As mentioned earlier, the disease follows a stable course for a variable length of time. During this period, treatment is primarily palliative. The main problems encountered are due to massive splenomegaly, anemia, bleeding diathesis, bone pain and hypermetabolism. Splenectomy, blood transfusion and oral hydroxyurea (to reduce tumour mass rapidly) are some of the treatment modalities undertaken to alleviate the symptoms. Allogenic bone marrow transplantation performed during the chronic phase has been curative in 50 per cent of patients.

The acute phase or blast crisis occurs as a terminal event. It resembles ALL but is resistant to antileukemic therapy. Death occurs within a few months after onset of the blast crisis.

Polycythemia rubra vera

Polycythemia rubra vera (PRV) is a hematologic malignancy characterised by the excessive proliferation of erythroid, myeloid and megakaryocytic elements in the bone marrow with an elevated peripheral blood count of the three major hematapoietic cell lines and an increased total red cell mass.

Pathophysiology The panmyeloerythroid hyperplasia results from clonal proliferation of

[1] Leukemoid reactions are 'leukemia-like' elevations of leukocyte counts seen in some conditions. These reactions do not represent malignant proliferation of leukocytes and frequently resolve as the underlying condition resolves. Infections (viral) are a common cause of these reactions.

the totipotent stem cell. The increased red cell mass is due to an unusual sensitivity of the abnormal erythroid precursor to circulating erythropoietin and is not due to increased levels of the latter. The major clinical features of PRV arise from various factors. Increased RBC mass leads to an increase in blood volume and increased viscosity. The increased blood volume predisposes to circulatory overload and the increased viscosity predisposes to vascular stasis and a thrombotic tendency. Erythremia and thrombocythemia further enhance the risk of thrombosis which can cause infarction of multiple organs systems, such as the heart, the kidneys and the spleen. Functional abnormalities of platelets and excessive distension of blood vessels causes hemorrhages within the gastrointestinal system, the oropharynx and the brain. Basophil proliferation and excessive histamine release accounts for the pruritus, as well as for the tendency for acid peptic disease commonly encountered in PRV. A high cell turnover gives rise to hyperuricemia with all its attendant complications. Hypermetabolism leads to weight loss, fatigue, lassitude and fever.

During the course of the disease, the proliferative phase of the disease 'burns out' giving way to progressive fibrosis of the bone marrow. Progressive enlargement of the liver and spleen develop, since extramedullary hematopoiesis occurs within these organs, and the bone marrow is replaced by fibrous tissue (myelofibrosis).

Clinical features The onset of PRV is insidious. The common presenting features are irritability, easy fatiguability, headache, abdominal fullness and pruritus. In rare cases, massive gastrointestinal hemorrhage or thrombosis of the coronary or cerebral arteries may be the first sign of the disease.

The physical examination reveals a ruddy (plethoric) and cyanosed appearance (stasis and deoxygenation of blood in the peripheral vessels are causative). Massive splenomegaly is a cardinal feature of the disease and accounts fo abdominal discomfort. Hepatomegaly is seen i 50 per cent of patients.

Investigation The Polycythemia Vera Stud Group criteria for the diagnosis of polycythemi vera has become a standard approach to th diagnostic problem. The criteria are shown i Table 15.32. The clinical approach to a patien with an elevated hematocrit is shown i Fig 15.19.

In 25 per cent of patients, CML or myeloi metaplasia with myelofibrosis occurs towar the 'burnt-out' phase of the disease. Occasio nally, AML develops as a terminal complicatio

Course Patients have a median survival o 10–20 years after the onset of the disease. Th medical complications most frequentl encountered arise mainly from the occurrence o vascular thromboses and hemorrhage. The include myocardial infarction, cerebrovascula accidents and heart failure, which are the mo frequent causes of death in this disease.

Treatment (Table 15.33) The mainstay o treatment is to reduce the circulating red ce mass to near normal levels by performin venesection. The repeated removal of 500 ml o whole blood every 2–3 days, until the hematocr stabilises at 55 per cent, is often followedb remission for several months. Risk of thrombos is high with this line of treatment and it therefore used with caution, particularly i elderly patients above 70 years of ag Radioactive phosphorus has been employed, bu the increased risk of AML with this drug ha curtailed its usage in patients below 50 years o age. Hydroxyurea (which is not toxic to the ste cell) has also been used for myelosuppression.

Myelofibrosis

In this variety of myeloproliferative disorder, th proliferation of the malignant myeloid stem cel occur mainly within the spleen (myelo

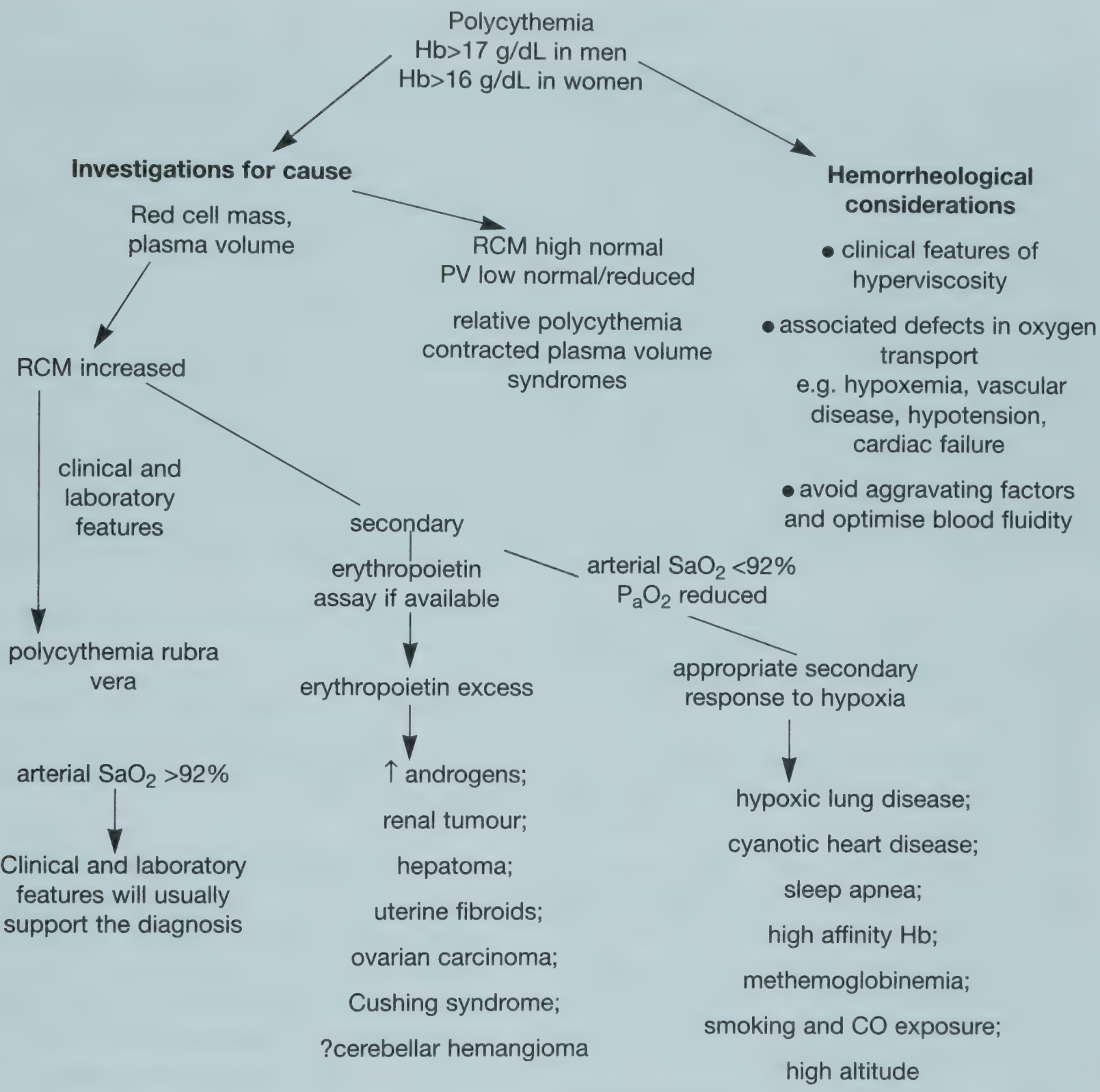

Fig 15.19 The investigation of polycythemia : RCM = red cell mass; PV = plasma volume; LAP = leukocyte alkaline phosphatase; LDH = lactate dehydrogenase; DPG = diphosphoglycerate

metaplasia), and the bone marrow is hypocellular and fibrotic (myelofibrosis).

The cause of extramedullary hematopoiesis and marrow fibrosis is unclear in most cases. Hence, it is described as idiopathic myeloid metaplasia. Sometimes myelofibrosis occurs following the 'burnt-out' phase of PRV or chronic myeloid leukemia.

Incidence This disease usually occurs after the age of 50 years.

Clinical features The disorder is brought to notice by anemia and progressive splenomegaly. Acute left upper quadrant abdominal pain arises from splenic infarction. Hyperuricemia and gout occur due to rapid turnover of blood

Table 15.32 Criteria for diagnosis of polycythemia rubra vera

Category		Category	
A1	Increased red cell mass in men > 36 ml/kg in women > 32 ml/kg	B1	Thrombocytosis Platelet count >400,000/mm^3
A2	Normal arterial oxygen saturation > 92%	B2	Leukocytosis >12,000/mm^3 (in the absence of fever or infection)
A3	Splenomegaly	B3	Increased leukocyte alkaline phosphatase > 100 (in the absence of fever or infection) Increased serum B_{12} (> 900 pg/ml) Increased unbound B_{12}-binding capacity (> 2200 pg/ml)
Diagnosis acceptable if the following combinations are present : A1 + A2 + A3 **or** A1 + A2 + any two from category B			

cells. Infections, bleeding tendency and transformation into acute leukemia are some of the other complications commonly encountered in this disease.

Investigations Tear drop-shaped RBCs are characteristic. Normoblasts with basophilic stippling, normal granulocytes, myeloblasts, myelocytes and metamyelocytes contribute to the leukoerythroblastic picture in the peripheral smear. Giant platelets and megakaryocytic fragments are highly suggestive of myeloid metaplasia with myelofibrosis. Demonstration of reticulin replacing the normal bone marrow in early cases, and bone marrow fibrosis, in late cases, is essential for the diagnosis of myelofibrosis. Absence of Philadelphia chromosome helps to differentiate it from CML.

Treatment Treatment is supportive. Regular blood transfusions prolong life in most cases. Hydroxyurea can be used to reduce leukocytosis and spleen size.

Primary Thrombocythemia

Primary thrombocythemia is an uncommon myeloproliferative disorder with clonal proliferation of the megakaryocytes. It occurs in elderly patients and is characterised by bleeding into the skin and mucosa as a result of platelet dysfunction and accelerated consumption of clotting factors. Venous emboli and vascular thrombosis, leading to gangrene of extremities

Table 15.33 Overall therapeutic recommendation of the Polycythemia Vera Study Group

Age group of patients	Treatment
>70 years	Radioactive phosphorus is used for myelosuppression and is supplemented by phlebotomy
<50 years	Phlebotomy and myelosuppression with hydroxyurea
50–70 years	Phlebotomy alone is optimal. Hydroxyurea is administered if myelosuppression is necessary.

also develop. Examination of the patient reveals anemia and splenomegaly. But there is no specific feature which is diagnostic of this disease.

Investigations Elevated platelet counts (>1000 × 10^9/L) with abnormally shaped platelets are seen in the peripheral blood smear examination. The bone marrow aspirate is hypercellular with megakaryocyte hyperplasia. The Philadelphia chromosome is absent. Infrequently, deletion of the long arm of chromosome 21 has been noted.

Treatment Treatment is symptomatic. If bleeding is severe or frequent, hydroxyurea can be administered to induce myelosuppression.

Prognosis Death occurs due to bleeding and thrombosis. Fifty per cent of patients survive for more than five years before succumbing to the complications of the disease.

MYELODYSPLASIA

The term myelodysplasia describes a heterogeneous group of stem cell disorders, characterised by marrow which is partly or wholly replaced by the clonal proliferation of stem cells which retain the capacity to differentiate into mature red cells, granulocytes and platelets, but do so in a way which is both ineffective and disordered. The result is that the bone marrow is hypercellular in the presence of pancytopenia.

Pathogenesis The blood cells and bone marrow show certain morphological and functional abnormalities. The detailed discussion of these is beyond the scope of this book.

Megaloblastoid RBC precursors, micro-megakaryocytes, hypogranular WBC precursors and increased blast cells are some of the bone marrow features. Deletions of the long arm of chromosomes 5, 7, Y, and trisomy 8 are some of the characteristic chromosomal anomalies seen in bone marrow aspirate studies in myelodysplasias. A classification of myelodysplasias is shown in Table 15.34.

Table 15.34 Spectrum of disorders in myelodysplastic syndrome

Refractory anemia with excess bone marrow blast cells (5–20% blasts, 1–2 years average survival)
Chronic myelomonocytic leukemia
Acquired sideroblastosis with dysplastic bone marrow (<5% blasts, 3–5 years average survival)
Aplastic or hypoplastic bone marrow with dysplastic features (<5% blasts, 2–4 years average survival)
Evolving or smouldering leukemia (20–30% blasts, <1 year average survival)

During the course of this disorder, the abnormal clone (which is unstable) loses its ability for normal cellular differentiation and transforms into an acute leukemia. Myelodysplastic syndromes were previously referred to as 'preleukemic leukemia' (Fig 15.20).

Incidence The disease typically occurs in males above 60 years.

Clinical features The commonest clinical features are due to anemia, severe recurrent infections and bleeding tendencies.

Investigations Peripheral pancytopenia, trilineage[1] dysplasia in a hyperplastic bone marrow with characteristic chromosomal abnormalities are diagnostic. Bilobed neutrophils (Pelger-Huet cells) may be seen in the peripheral smear.

Treatment Intensive chemotherapy followed by bone marrow transplantation from an HLA-matched sibling is curative in a small number of patients.

1 'Trilineage' refers to 'three' cell lines: red cells, granulocytes and platelets.

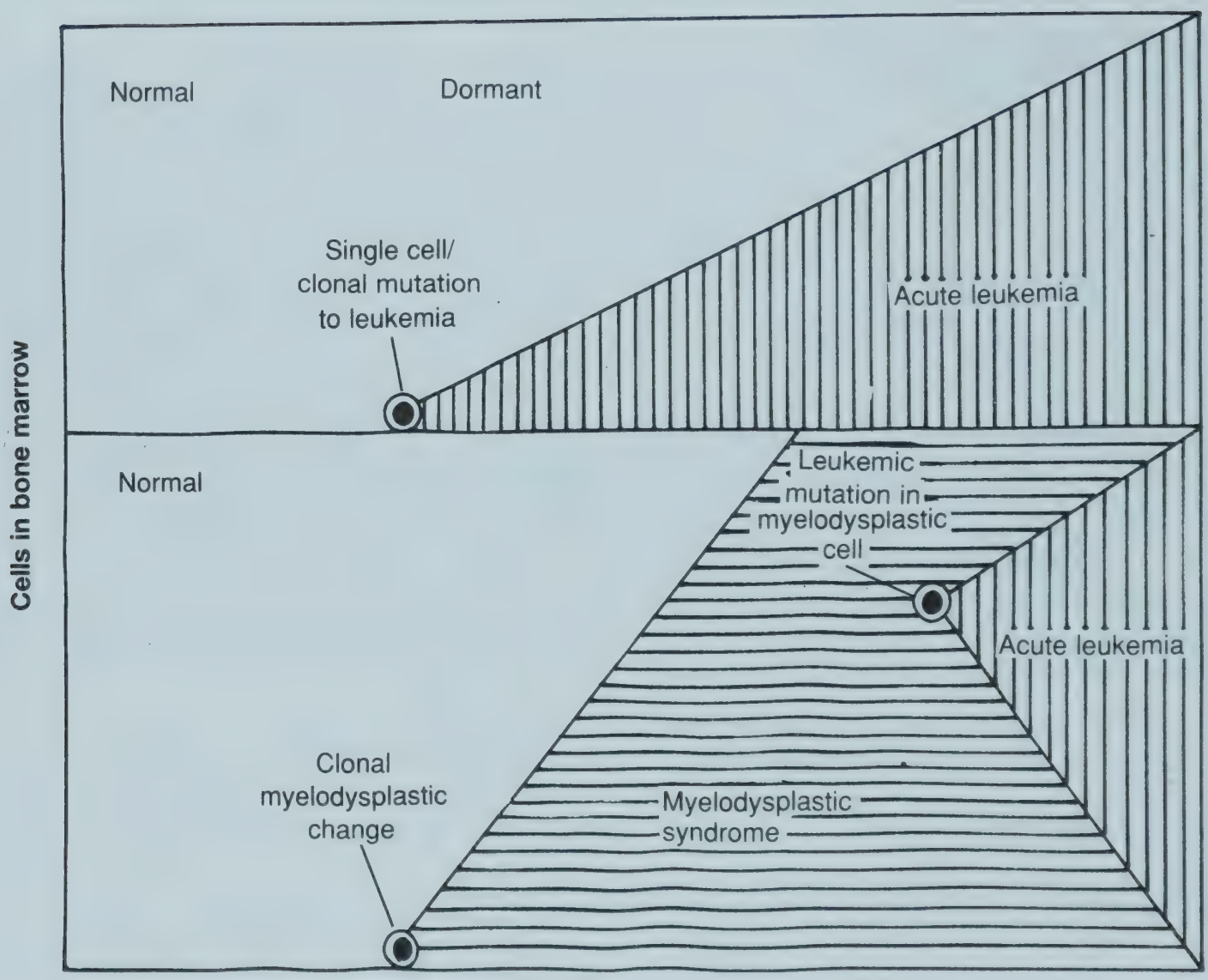

Fig 15.20 The myelodysplastic syndrome and the evolution of leukemia

Plasma Cell Dyscrasias

Plasma cell dyscrasias are characterised by an uncontrolled, clonal proliferation of the plasma cell-lymphocytic series, with the production of excessive, homogeneous immunoglobulins or immunoglobulin fragments.

Pathophysiology In plasma cell dyscrasias, the neoplastic B cell lymphocyte is differentiated sufficiently enough to secrete immunoglobin of a single molecular species, all molecules within this population being identical. These homogeneous immunoglobulins are referred to as the *M spike component* in serum. In multiple myeloma, the immunoglobulin is usually of IgG, IgA or IgE type. In a significant proportion of patients, kappa or lambda (L) light chains or heavy chains alpha, gamma or mu are produced. The light chains are small enough to be filtered by the glomerulus, that is, Bence-Jones[1] urinary proteins. In such patients the 'M component' is absent in serum. However, in the majority of patients the malignant cells, synthesise both the complete immunoglobulin, as well as, excess incomplete L or H chains.

Classification Based on the type of immunoglobulin and the clinico-anatomic behaviour of the neoplastic cells, plasma cell dyscrasias can be classified into five categories :

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[1] Bence-Jones proteins are immunoglobulin (L) chains which are filtered by the renal glomerulus. When the catabolic capacity of the tubule is exceeded, the excess protein appears in the urine. These are peculiar in that they precipitate at 40°C–60°C and redissolve when heated to 95°C–100C°.

1. multiple myeloma,
2. Waldenstrom's macroglobulinemia,
3. heavy chain disease,
4. primary or immunocyte-associated amyloidosis, and
5. monoclonal gammopathy of undetermined significance.

Etiopathogenesis It has been postulated that this group of disorders results from two separate, instigating factors occurring concurrently. Prolonged antigenic stimulation leads to 'turning on' of the B cell. This provides an opportunity for a spontaneous mutation to occur, leading to uncontrolled growth of the affected clone of B cells.

Multiple myeloma

Incidence The peak age of incidence of multiple myeloma is between the age of 50–60 years. Both males and females are affected equally.

Pathology and pathophysiology (Fig 15.21) The pathologic effects of this tumour are due to the excessive, biologically ineffective immunoglobulins and the destructive capability of the neoplastic cells. The abnormal aggregates of plasma cells infiltrate the bone marrow, the skeletal system, the kidneys and the nerve roots.

Multifocal, destructive lesions within the cortical bones appear as 'punched out' defects. These are produced by *osteoclast activating*

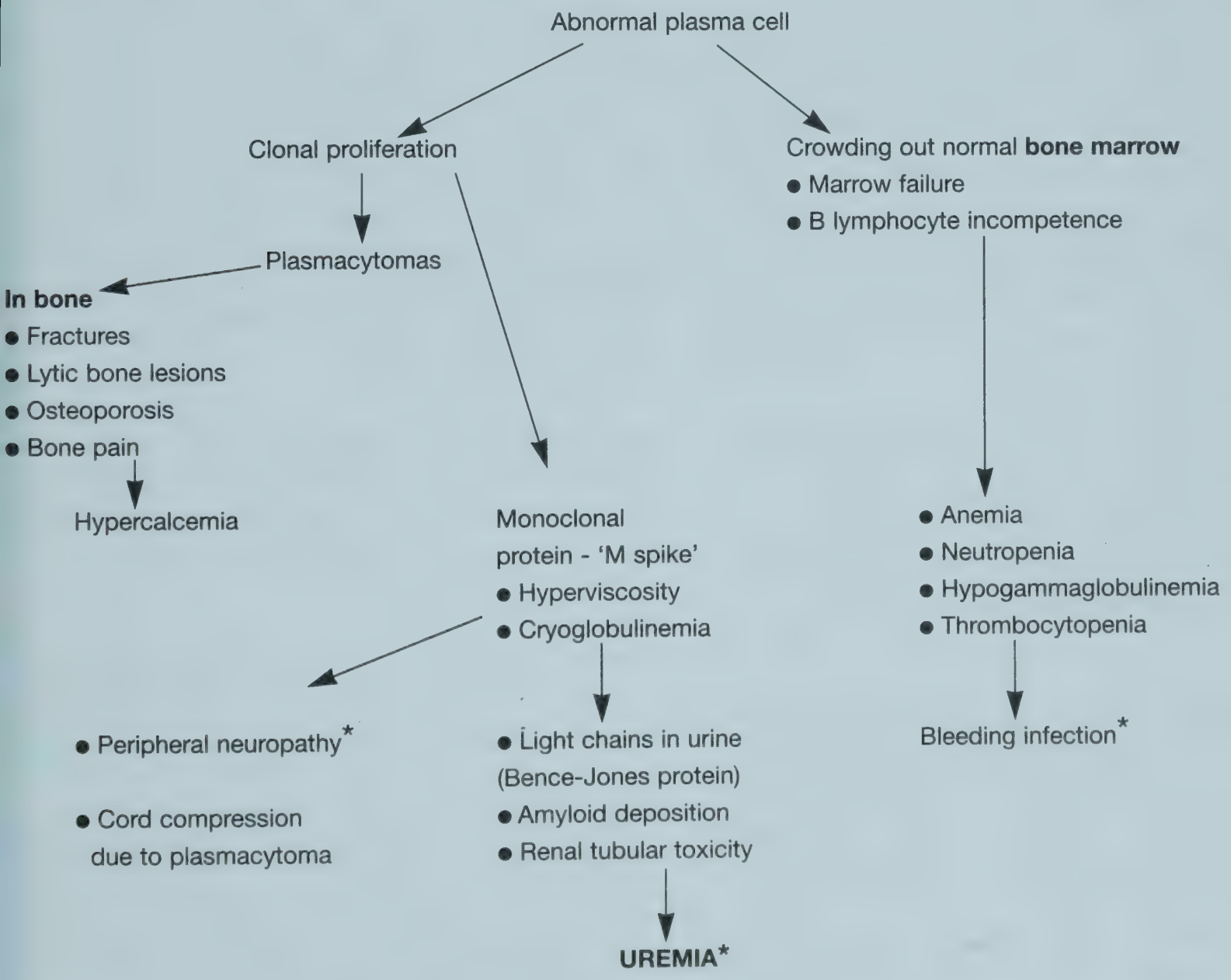


Fig 15.21 The pathology of multiple myeloma : * = presenting complaints

factors which are secreted by the myeloma cells. Renal damage results from both direct infiltration of the kidney by the neoplastic cells, as well as by the excess of plasma protein which is filtered by the glomerulus. Proteinaceous casts (which are either light or heavy chains, or even complete immunoglobulins) fill the collecting and distal tubules and cause a chronic interstitial nephritis with tubular atrophy. This leads to progressive renal damage.

Metastatic calcification (secondary to skeletal destruction) and hypercalcemia are additional factors contributing to myeloma nephropathy.

Tumour infiltration of nerve trunks and vertebral collapse secondary to lytic lesions can cause neurologic complications. Infiltration of the bone marrow results in progressive marrow failure, while recurrent infections occur due to deficiency of normal immunoglobulins. Abnormal plasma globulins aggregate within the circulating plasma and cause a hyperviscosity syndrome.

Clinical features Bone pain is the most common presenting complaint. Pathologic fractures and collapse of the demineralised vertebrae can produce spinal cord and nerve root compression.

Severe anemia occurs due to marrow suppression. It is exacerbated occasionally by a Coomb's positive hemolytic anemia or by coexistent renal insufficiency. Rarely, spilling over of the plasma cells into the peripheral blood results in *plasma cell leukemia*, which is rapidly fatal.

Investigations Diagnosis of multiple myeloma depends on the demonstration of punched out '*soap bubble*' lesions in the bones (axial skeleton), the detection of monoclonal immunoglobulins in serum and/or urine (by electrophoresis), and the demonstration of the myeloma cells in bone marrow biopsy. A staging system proposed is shown in Table 15.35 (for 'Treatment' see end of section).

Waldenstrom's macroglobulinemia

Incidence It is a rare disorder seen above the age of 50 years, with a peak incidence between 60 and 70 years. It is twice as common in men.

Pathology This disease results from the neoplastic proliferation of a single clone of lymphocytes, plasma cells or lymphocytoid plasma cells which infiltrate the reticulo endothelial system and synthesise homogeneous IgM, thereby leading to macroglobulinemia.

Clinical features Non-specific complaints like weakness, fatiguability and weight loss are the usual presenting features. *Hyperviscosity syndrome* occurs due to the aggregation of the IgM paraproteins. This leads to prolonged oozing from wounds, visual impairment, neurologic symptoms like headache, alteration in sensorium, dizziness and deafness. Precipitation of the proteins at low temperature gives rise to *cryoglobulinemia*[1] which is characterised by Raynaud's phenomena and 'cold urticaria'. On examination lymphadenopathy and hepato-splenomegaly are the protean clinical findings. A comparison of clinical features with those of multiple myeloma is shown in Table 15.36.

Investigations Demonstration of monoclonal IgM (>3000 mg/dl) associated with abnormal accumulation of lymphocytoid cells in the bone marrow is considered diagnostic.

Heavy chain diseases

Heavy chain diseases are rare lympho proliferative disorders characterised by the presence of immunoglobulin fragments related

[1] Monoclonal IgM has the property of 'gelling' or precipitating at a temperature lower than body temperature (cryoglobulinemia). Affected patients present with palpable purpura and Raynaud's phenomenon. Progressive renal insufficiency is quite common, especially in the presence of Bence-Jones proteinuria. Recurrent infections, such as pneumonia, urinary tract infection or meningitis occasionally bring this disorder to notice.

Table 15.35 Myeloma staging system

Stage	Criteria	Myeloma cell mass ($x10^{12}$ cells/m^2)
I	All of the following : 1. Hemoglobin value > 10 g/dl 2. Serum calcium value (≤12 mg/dl) 3. On X-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only 4. Low M-component production rates a. IgG value < 5 g/dl b. IgA value < 3 g/dl c. Urine L chain M-component on electrophoresis <4 g/24 hours	<0.6 (low)
II	Fitting neither Stage I nor Stage III	0.6–1.20 (intermediate)
III	One or more of the following : 1. Hemoglobin value <8.5 g/dl 2. Serum calcium value >12 mg/dl 3. Advanced lytic bone lesions (scale 3) 4. High M-component production rates a. IgG value >7 g/dl b. IgA value > 5 g/dl c. Urine L chain M-component on electrophoresis > 12 g/24 hr	>1.20 (high)
Subclassification :		
A = Relatively normal renal function (serum creatinine value <2.0 mg/dl)		
B = Abnormal renal function (serum creatinine value ≥2.0 mg/dl)		
Examples :		
Stage IA = Low cell mass with normal renal function		
Stage IIIB = High cell mass with abnormal renal function		

to heavy (H) chains in the serum and urine. *Alpha chain disease* is characterised by massive lymphomatous infiltrations of the intestines and abdominal lymph nodes. *Gamma chain disease* involves the lymph nodes and spleen. *Mu chain disease* causes skeletal destruction and bone marrow and retroperitoneal node infiltration.

Primary amyloidosis

See Chapter 17.8.

Monoclonal gammopathy of undetermined significance

This is defined as dysproteinemia without associated disease. Such patients have less than 3 g/dl of monoclonal protein, no Bence-Jones proteinuria and less than 5 per cent of plasma cells in the bone marrow. When followed up for 15–20 years, 20 per cent developed features of plasma cell dyscrasias.

Treatment of plasma cell dyscrasias

Supportive treatment is necessary when complications secondary to paraproteinemia arise (Table 15.37).

Specific treatment : Alkylating agents such as melphalan and cyclophosphamide are the mainstay of treatment for myeloma. Melphalan (8 mg/m^2) and prednisolone (100 mg/m^2) for four days every 4–6 weeks is a common regimen.

BCNU, adriamycin, vincristine and alpha interferon are also being used in refractory cases. Pulse doses of steroids with alkylating agents are also helpful. Bone marrow transplantation has helped prolong life.

Waldenstrom's macroglobulinemia: The hyperviscosity is often managed only with plasmapheresis. Alkylating agents like

Table 15.36 Comparison of clinical features of two common plasma cell dyscrasias

Clinical features	*Multiple myeloma*	*Waldenstrom's macroglobulinemia*
Fever	Rare (without infection)	Frequent (unrelated to infection)
Lymphadenopathy	Infrequent	Modest enlargement
Hepatosplenomegaly	Infrequent in absence of amyloidosis	Modest enlargement
Bone pain	Common	Uncommon
CNS involvement	Root pain and/or paraparesis	Encephalopathy, myelitis, neuropathy
Bleeding tendencies	30% of cases	50% of cases
Amyloidosis	5–15%	5%
Renal failure	Common	Infrequent
Investigations		
Electrophoretic pattern	IgG – 55%, IgA – 20%, light chain 25%	IgM> 3000 mg/dl
Peripheral smear	Rouleaux formation	Rouleaux formation
Bone marrow	Infiltration	Infiltration
ESR	Increased	Increased
Bence-Jones proteinuria	> 50%	40%
Bone scan	Lytic lesions	No abnormality
Serum calcium	Increased	No abnormality
Hyperviscosity syndrome	Rare	Common

chlorambucil, cyclophosphamide and melphalan are useful in 40 per cent of patients in reducing tumour mass and plasmapheresis requirement.

Prognosis in plasma cell dyscrasias Median survival for patients with multiple myeloma is three years. Risk factors which shorten survival are anemia (hematocrit <25%), IgG spike > 7g/dl, renal failure, hypercalcemia (>12 mg/dl) hypoalbuminemia, plasma cell leukemia, failure to respond to therapy, rapid progression of illness, and presence of three or more lytic bone lesions.

Waldenstrom's macroglobulinemia: Patients being treated for this disorder and who are responsive to chemotherapy survive for a median duration of four years. Non-responders survive for only two years.

Table 15.37 Supportive treatment in plasma cell dyscrasias

Symptom	*Therapy*
1. Bone pain	Focal radiotherapy and appropriate orthopedic procedures which enable early ambulation
2. Bone marrow failure	Blood component therapy
3. Infections	Appropriate antibiotics
4. Progressive renal failure	Peritoneal or hemodialysis
5. Hypercalcemia	Rehydration, steroids, mithramycin
6. Hyperviscosity	Plasmapheresis

KEY CONCEPTS

Acute leukemia

- This is a group of disorders characterised by uncontrolled proliferation of malignant cells derived from one of the hemopoietic precursors (myeloid stem cells in acute myeloid leukemia [AML]; lymphoid stem cells in acute lymphocytic leukemia [ALL].
- Symptoms are due to replacement of the normal bone marrow with malignant cells and due to dysfunction of the blood elements.
- Etiologic factors include radiation, exposure to toxins, cytotoxic drug use and viral infections.
- ALL is more common in children (peak incidence at 3–5 years). It presents with generalised lymphadenopathy, splenomegaly, bone pain and signs of bone marrow failure (pallor, bleeding tendency, infections).
- AML is common in the young and in middle-aged adults (45–55 years). Patients present with infections, bleeding (ecchymoses, petechiae) and occasionally, with gingival infiltration. Adenopathy is unusual; splenomegaly is less common than in ALL.
- Key laboratory investigations include peripheral blood smear examination and bone marrow biopsy; cytochemical staining, immunophenotyping and cytogenetic studies help differentiate ALL from AML. Generally, myeloblasts have cytoplasmic Auer rods and stain positive for myeloperoxidase. Lymphoblasts do not have Auer rods or myeloperoxidase but stain positive for the enzyme terminal deoxynucleotidyl transferase (TDT). Three ALL subtypes and 8 AML subtypes are recognised.
- General supportive measures include maintaining adequate Hb levels (transfusion with packed red cells), preventing hemorrhage (platelet transfusions) and controlling infections (isolation, barrier nursing, surveillance and treatment, granulocyte infusions).
- ALL: initial induction is with vincristine, prednisone and L-asparaginase; consolidation and maintenance is with 6-mercaptopurine and methotrexate. Potential sanctuary sites include the CNS and the testes; prophylaxis is instituted with craniospinal and gonadal irradiation and intrathecal chemotherapy. Remissions occur in over 90% and bone marrow transplantation must be considered after the first remission. Young age, female sex, low white cell counts, L-1 morphology and absence of CNS disease are good prognostic factors.
- AML: Induction is with cytosine arabinoside, anthracyclines, with or without 6-thioguanine. Remission occurs in 60–70% although it is long lasting in fewer than 30%. Allogenic bone marrow transplantation from an HLA-matched sibling in the first remission increases the cure rate to over 50%. The M-3 subtype is unique in that it responds to all trans retinoic acid.
- Autologous harvested and stored marrow (during periods of remission) is being increasingly used.

Chronic lymphocytic leukemia

- CLL is a disease characterised by neoplastic proliferation of the mature lymphocytes; about 70% are of B cell origin, 5% are of T cell origin, while the rest are of null cell type. It is a disease of the elderly (>60 years).
- Clinically, CLL evolves from an initial asymptomatic phase with peripheral blood lymphocytosis into a stage with generalised lymphadenopathy. Later splenomegaly appears. Eventually, with bone marrow involvement and failure, anemia and thrombocytopenia may develop. CLL is associated with increased susceptibility to infections and patients may develop an autoimmune hemolytic anemia.
- The diagnosis is based on the peripheral blood smear examination and bone marrow biopsy.
- No definite treatment is required for the patient with only lymphocytosis or asymptomatic lymphadenopathy. With evolution of splenomegaly, treatment is initiated with chlorambucil, with or without steroids; fludarabine is being evaluated in CLL. Splenic irradiation and leukapheresis are adjuncts.
- Death in CLL is usually due to bone marrow failure and intercurrent infections (median survival 10 years). The prognosis is worse for T cell CLL. Blastic transformation is uncommon.

Hodgkin's disease

- Hodgkin's disease is a chronic disease due to neoplastic proliferation of cells of the lymphoreticular system. It is characterised by the presence of large multinucleate reticulum cells (*Reed-Sternberg cells* with mirror image nuclei) which are probably of mononuclear origin.
- The disease has a bimodal incidence (peaks at 15–30 years and >50 years). There are four subtypes: nodular sclerosis, mixed cellularity, lymphocyte predominant, lymphocyte depleted. Most patients have reduced T cell function.
- Lymphadenopathy is the cardinal feature; lymph nodes are enlarged, non-tender, and rubbery. Lymphadenopathy is asymmetrical and often unilateral because the disease spreads in a contiguous fashion. Additional systemic features include fever (Pel-Ebstein pattern occasionally), drenching night sweats, weight loss and

pruritus; these are referred to as B symptoms (except for pruritus) and have prognostic importance.

➢ Staging of the disease uses a standard classification (Ann Arbor) and involves obtaining a chest X-ray, CT or US scan, lymphangiography, liver and splenic scans (gallium), and a staging laparotomy (in most patients who do not have unequivocal Stage III/IV disease). Subjects with bone marrow involvement show disproportionate pancytopenia.

➢ Treatment of Stage I/II disease is with extended field radiotherapy (mantle field supradiaphragmatic, inverted Y field infradiaphragmatic; 80% 5-year survival). Stage III disease may be treated with total nodal radiation and chemotherapy. Patients with Stage III and IV disease are managed with systemic chemotherapy (MOPP alternating with ABVD; 50% 5-year survival). If there is bulky mediastinal disease, (>1/3 of chest diameter on X-ray) combined radiation and chemotherapy is recommended (irrespective of the stage).

➢ Bone marrow transplantation may be used in select patients. Absence of B symptoms and lymphocyte predominant or nodular sclerosis histologies indicate a favourable prognosis.

Non-Hodgkin's lymphoma

➢ This is a heterogeneous group of disorders characterised by neoplastic proliferation of lymphoid cells; 80% of NHL are B cell type, 15% are of T cell origin, and 5% are true histiocytic neoplasms.

➢ Predisposing conditions include radiation, chemical toxins, viral infections (Epstein-Barr virus), immunodeficiency (primary, SLE, HIV) and chromosomal abnormalities (translocation of chromosome 9).

➢ Histologically, three categories are recognised:

low grade (40%; follicular, small cleaved, and mixed; predominantly B cell; favourable prognosis, median survival 5–7 years)

intermediate grade (40%; mostly diffuse large cell; both T and B cell; extranodal masses; intermediate prognosis, median survival 2–3 years)

high grade (20%; lymphoblastic, diffuse small non-cleaved, adult T cell; marrow and CNS spread with leukemic phase; unfavourable prognosis, median survival <2 years)

➢ NHL is characterised by widespread dissemination due to blood-borne and lymphatic spread. NHL differs from Hodgkin's disease in its non-contiguous spread, presentation with nodal masses and involvement of the epitrochlear lymph nodes and the Waldeyer's ring.

➢ Clinical features include malaise, weight loss, fever, lymphadenopathy (often bilateral, generalised) and hepatosplenomegaly. Opportunistic infections are common due to depressed immune responses.

➢ Investigations include lymph node biopsy, bone marrow aspiration and biopsy, imaging studies (CT scan of abdomen); diagnostic laparotomy is less important than for Hodgkin's disease. A staging system similar to Hodgkin's lymphoma is used (Ann Arbor):

low grade: Stage I–II: total nodal irradiation;

advanced stages: chemotherapy (chlorambucil or cyclophosphamide with or without prednisone) + radiation

intermediate grade: combination chemotherapy + radiation + intrathecal CNS prophylaxis; non-Burkitt diffuse, small, non-cleaved: as for intermediate grade; T cell: chemotherapy; Burkitt's debulking + chemotherapy

Chronic myeloid leukemia

➢ CML is a neoplastic proliferation of mature cells of the myeloid series. Translocation of a part of the long arm of chromosome 9 (abl) on to the long arm of chromosome 22 (bcr) is central to the pathogenesis; this translocation appears as the Philadelphia chromosome, which is pathognomonic of CML.

➢ It is a disease of the young and middle aged. Presenting complaints include weight loss, malaise, pallor, bleeding and infections. On physical examination the striking finding is a moderate to large splenomegaly. Lymphadenopathy is not a prominent feature.

➢ Laboratory investigations reveal an elevated leucocyte count (usually >100,000 x 10^9/L), a peripheral smear with mature leucocytes as well as a few immature cells of the myeloid series, an elevated uric acid level and a low leucocyte alkaline phosphatase (LAP) level.

➢ The natural history is marked by a 50 per cent rate of blast transformation (into AML), a condition associated with a very high mortality.

➢ Management includes treatment of anemia (transfusions), control of elevated white cell counts (busulphan and hydroxyurea, splenectomy, α-interferon), and treatment of intercurrent infections. Allogenic bone marrow transplantation must be considered in patients who are younger than 45 years.

Polycythemia rubra vera

➢ Polycythemia may be primary (PRV, autonomous production of erythrocytes), secondary (*hypoxia*: cardiac, respiratory disease, obesity; *exogenous production of erythropoietin*: renal, hepatic tumours) or relative (reduced plasma volume as in dehydration).

- PRV is a disease of middle age (50–70 years). Clinical manifestations include lethargy, pruritus, headaches, visual disturbances, dyspepsia and gout. Findings on physical examination include a plethoric appearance, hypertension, engorged retinal veins and splenomegaly.
- Diagnosis is based on a set of criteria. *Major criteria*: increased red cell mass (>36 ml/kg in men, >32 ml/kg in women), arterial oxygen saturation ≥92%, splenomegaly. *Minor criteria*: increased urate, leucocyte alkaline phosphatase (LAP), vitamin B_{12} (>900 pg/ml).

  Diagnosis is based on presence of three major criteria or of the first two major criteria + two minor criteria.
- Treatment measures include repeated phlebotomy (to maintain a hematocrit of <50%) and myelosuppression (hydroxyurea; radioactive ^{32}P only in the elderly). Allopurinol may be helpful for gout prophylaxis and treatment while antihistamines may relieve pruritus.

Myelofibrosis

- This is a disorder of clonal stem cells characterised by an increase in fibrous tissue within the bone marrow along with myeloid metaplasia (marrow stem cells appear in abnormal sites such as the liver and the spleen).
- The symptoms of disease are non-specific and include fatigue, malaise, and weight loss. Physical examination reveals anemia and massive splenomegaly.
- The peripheral blood smear shows a leucoerythroblastic picture with tear drop red blood cells. There may be associated leucocytosis and thrombocytosis. Serum levels of uric acid, and leucocyte alkaline phosphatase are elevated. The bone marrow aspirate is often dry but multiple biopsies confirm the pressence of marked fibrosis.
- Treatment modalities include blood transfusions for symptomatic relief, androgens (to stimulate erythropoiesis), folate supplementation and allopurinol for gout. Alpha-interferon can reduce splenic size, although occasionally splenectomy may be required. Myelofibrosis may transform into an acute leukemia in 5–10% of patients.

Myelodysplastic syndromes

- This category includes a spectrum of clonal disorders characterised by progressive bone marrow failure and a varying combination of anemia, leukopenia and thrombocytopenia.
- Elderly patients are most often affected and present with fatigue, weight loss, infections and bleeding tendencies.
- At least four subtypes are described with differing prognosis. Upto a third of patients go on to develop an acute leukemia.
- Bone marrow transplantation must be considered as an option in the young patient. Other treatment modalities include transfusions with packed red cells, administering of colony stimulating factors and pyridoxine use.

Multiple myeloma

- Myeloma is a neoplastic proliferation of mature plasma cells within the bone marrow. One of the hallmarks of the condition is the secretion of monoclonal immunoglobulins by the tumour cells; these monoclonal Ig appear in plasma (as an M spike on electrophoresis) or the light chains are filtered by the kidneys into the urine (Bence-Jones proteins).
- Myeloma is a disease of the elderly (seventh decade). Symptoms are due to bone involvement (pathologic fractures, back pain, nerve root pains), an increased susceptibility to infections and hyperviscosity (purpura, ecchymoses, headaches, fundal hemorrhage, digital gangrene). Renal involvement is frequent (infiltration, hypercalcemia, amyloid, hyperuricemia) and renal failure occurs in about 50 per cent.
- Laboratory findings include markedly elevated ESR, hypercalcemia, increased alkaline phosphatase, M spike in plasma and urinary Bence-Jones protein. A skeletal X-ray shows generalised osteoporosis, and osteolytic lesions in the skull (*pepper pot skull*), pelvis, spine and ribs. Urea and creatinine levels are elevated in patients with renal failure.
- The bone marrow biopsy reveals more than 30 per cent plasma cells. A radioscintiscan of the skeleton may reveal additional areas involved. Staging is based on hematologic parameters (Hb), immunoglobulin levels, and the extent of skeletal involvement. Staging correlates well with tumour burden.
- Indolent or Stage I myeloma need not be treated but should be monitored for disease progression. For progressive disease (median survival 2–3 years), chemotherapy (melphalan with or without doxorubicin, vincristine, prednisone) is the therapeutic modality of choice. Alpha-interferon may have a role in maintenance. Radiation has a role for localised skeletal disease. Disodium etidronate and gallium nitrate may inhibit bone resorption. Surgery or radiation are options for treating plasmacytomas.
- Adverse prognostic factors include renal failure, elevated β_2 microglobulin and severe anemia.

15.8 Transfusion medicine

Blood Groups

Human red blood cells carry the blood group antigens (usually glycolipids or proteins) on their surface. The inheritance of these blood group antigens follows Mendelian genetics.

About 400 different blood antigens have been identified so far, of which the ABO and Rhesus antigens are the most important in clinical practice. The expression of ABO blood group antigens results from the presence of allelic genes ABO and H. The H gene encodes an enzyme which attaches fructose to a basic glycoprotein molecule named *substance H*. The latter is a precursor of A and B blood group antigens. When N-acetyl galactosamine is added to substance H, an 'A' group antigen results.

On addition of D-galactose to substance H, a 'B' group antigen results. Enzymes responsible for these actions are coded for by the A and B genes respectively. The O gene does not alter substance H. Therefore, the O blood group results from the absence of A or B antigens and is not due to the presence of a specific antigen. Individuals who lack the H gene therefore cannot produce A, B or O antigens; a rare blood group type called the *Bombay group* results.

Antibodies to A and B antigens are present in human plasma. They occur naturally as anti-A and anti-B. These develop in the first few months of life, without apparent A or B blood group antigens on the surface of the red blood cells. These antibodies are of the IgM variety. Immune antibodies can also develop on exposure to blood group antigens not present on the individual's own red blood cell. Such a situation may arise following an 'incompatible' transfusion or following the transplacental contamination of maternal circulation with fetal red cell antigens during pregnancy.

Immune antibodies, which occur following exposure to a foreign blood group antigen, belong to the IgG group. The latter, unlike the IgM antibodies, can cross the placenta during pregnancy and cause the hemolytic disease in the newborn. It is mandatory, therefore, to type a patient's blood group antigen (A, B, AB or O) with the help of the specific antisera available for this purpose.

The Rhesus Blood Group System

The Rhesus (Rh) system was first demonstrated in 1940 when it was shown that an antibody against the red cells of the Rhesus monkey (which had been produced in rabbits) would agglutinate the red cells of approximately 85 per cent of humans (Rh positive) but would not agglutinate the red cells of the remaining 15 per cent (Rh negative). The Rh group is believed to be determined by three sets of allelic genes. These are designated as C and c, D and d, and E and e (*Fisher nomenclature*). Since only one of each pair of genes can be carried on each chromosome from the parents, 36 genotypes are possible. CDe, cde, CDE, cDE, cDe, cdE, CdE and Cde are the commonly occurring genotypes. The most potent and clinically important Rh antigen is coded by D and in practice

Rh grouping is performed by using the anti-D antibody. As a result of this test, the persons being grouped are classified as Rh positive or Rh negative. The subject may be homozygous Rh positive (DD) or heterozygous Rh positive (Dd). There is a variation in the ability to provoke anti-D antibodies (dosage effect). Naturally occurring anti-D antibodies are rare, but they can be produced by the transfusion of Rh positive blood or by the transplacental leakage of Rh positive blood from the fetus. Maternofetal blood incompatibility can result in severe hemolytic disease of the newborn.

As mentioned earlier there are several other blood group systems. Kell (K), Duffy (Fy), Kidd (JK) are some important antigenetic types but will not be discussed in this text.

White cell groups

White cells carry very small amounts of ABO antigens. Of greater importance is the presence of human leukocyte antigens (HLA) which are present on WBCs and a host of other body cells. Since antibodies to the HLA system do not occur naturally and develop only after repeated transfusions, they are not routinely investigated prior to blood transfusion in clinical practice. Antibodies to these antigens cause febrile reactions and in such patients, leukocyte-poor blood or 'washed red cells' may be used.

Platelet groups

Platelets can carry ABO, HLA and platelet-specific antigens (Pl^{A1}); all these can induce antibodies of IgG type. The latter can destroy platelets to cause thrombocytopenia.

Transfusion

Transfusion is a form of replacement therapy. It may involve replacing whole blood or a particular component of blood. The separation of blood components from whole blood is partly by centrifugation, alteration of temperature and partly by chemical processes.

Red cell concentrates

Plasma is removed from whole blood. The resultant unit of red cells has a hematocrit of 80 per cent in a volume of 300 ml. These packed 'cells', as they are also known, are administered to patients with chronic anemia or where blood volume loss is less than 1500 ml. Transfusions of red cell concentrate improves oxygen delivery to the tissues without causing volume expansion with all its attendant complications. When there is loss of whole blood, red cells and volume are replaced simultaneously. Severe hypovolemia can result in shock, renal failure and disseminated intravascular coagulation. These complications can be averted by quick administration of fresh whole blood.

Stored whole blood is a poor source of factor VIII and V. Other coagulation factors are stable in stored blood. In emergency situations resulting from acute hemostatic failure, administration of whole blood can maintain adequate levels of clotting factors (other than V and VIII) in the absence of liver cell failure

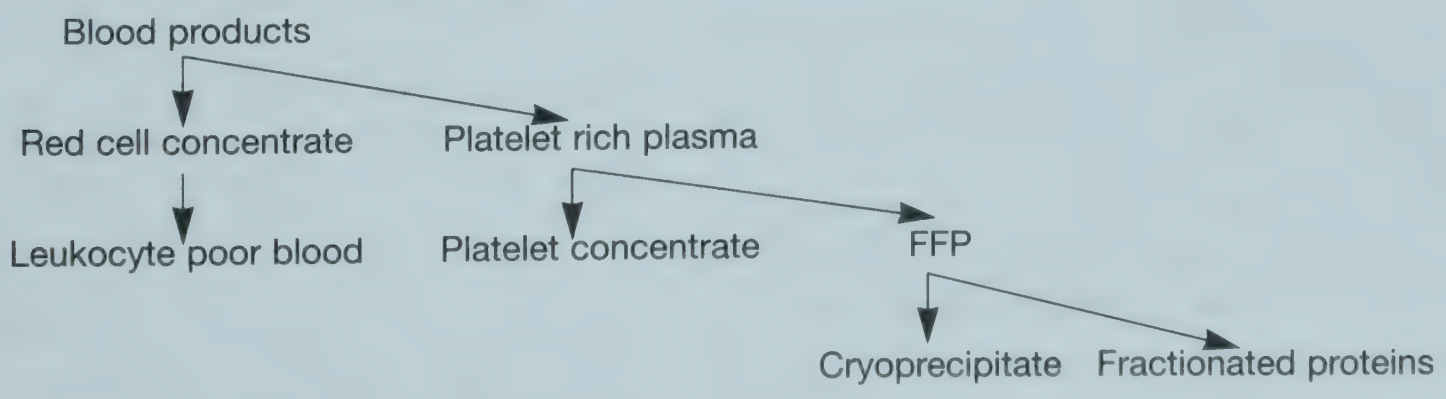


Fig 15.22 Blood products

Table 15.38 Changes in stored blood at 2–6°C for 21 days

Red cells	Viability falls to 75–80%; variable fall in ATP and 2,3-DPG
White cells	Loss of neutrophil function in 24 hours
Platelets	Not viable after 24–36 hours
Electrolytes	Plasma potassium increases from 4 mmol/L to 20 mmol/L; there is an increase in lactic acid and ammonia
Plasma hemoglobin	Rises from 1 ng/dl to 20 ng/dl
Coagulation factors	Factors V and VIII: less than 10% after 24 hours; Factors IX and X: less than 10% after 1 week (21 day old blood cannot correct clotting defects)
pH	Falls from 7.3 to 6.7
pCO_2	Rises from 45 mmHg to > 100 mmHg

and disseminated intravascular coagulation (DIC).

Platelet concentrates

In the allo-immunised patient HLA-matched platelets (5–10 units) are obtained from a single donor by platelet pheresis. Since extensive extracorporeal processing and reinfusion are necessary, the platelet obtained by platelet pharesis should be administered within twenty-four hours after collection. ABO incompatibility is not a significant problem in platelet transfusions.

Indications for platelet transfusion

Emergency conditions: Platelet count < 40,000/mm^3 with clinical evidence of hemorrhage

Prophylactic therapy:

Platelet count < 20,000/mm^3 with severe bone marrow failure

1. Prior to invasive procedures to maintain platelet count at 80,000/mm^3 for major surgery (laparotomy)
2. To maintain platelet count at 40,000/mm^3 for minor procedure (spinal tap, endoscopy)

Contraindication Disorders of increased platelet consumption are contraindications for platelet transfusion.

Fresh frozen plasma

Fresh frozen plasma (FFP) from donors is now in common usage. It is defined as the fluid portion of a unit of blood which has been centrifuged, separated and frozen within six hours of collection. When stored at –30°C, it has a shelf life of one year. FFP contains labile and stable components of the coagulation, fibrinolytic and complement systems. It also contains proteins necessary to maintain oncotic pressure and immunity. Hence FFP is useful in the treatment of coagulation factor deficiencies of both acquired and congenital origin like DIC, chronic liver disease and hemophilia. FFP can also be used in hypovolemia when whole blood is not readily available.

Ideally the donor and recipient should be ABO and Rh compatible.

Granulocyte transfusion

Granulocytes cannot be separated from routine donor blood. 6–8 litres of blood processed during 2–3 hours by centrifugal blood cells separation can yield a granulocyte concentrate. Donors have to be premedicated with agents which cause rouleaux formation of RBCs to enable separation of granulocytes from RBCs. Marginated WBCs are mobilised by

administration of steroids. The lifespan of granulocytes is short (about eight hours). Hence, they should be transfused as soon as possible.

Granulocyte transfusion is indicated when the absolute granulocyte count decreases to 500/mm^3 in the presence of sepsis due to multiple antibiotic resistant strains. It has also been used in neonatal septicemia.

Prothrombin complex

FFP can be used in the treatment of vitamin K dependent factor deficiencies such as II, VII, X as is common in liver disease. However, circulatory overload and citrate toxicity curtail its use. Stable concentrates of prothrombin complexes are now available and can effectively control bleeding produced by liver disease or anticoagulants.

Fibrinogen

Fibrinogen can be obtained from cryo-precipitate. It has been found useful in DIC, but FFP and whole blood are more effective.

Purified protein fraction

This is prepared from pooled plasma after removal of cryoprecipitate. It contains 4–5 g/dl of protein, 90 per cent which is albumin. It has 145 mmol/L of sodium and 2 mmol/L of potassium. It contains no fibrinogen or A and B agglutinogens. All these properties make it a useful plasma expander particularly in the treatment of burns. Cryoprecipitate is produced from individual donations by allowing FFP to thaw at 4°C, over a period of 18–22 hours. The supernatant is removed by centrifugation. The resultant precipitate (10–20 ml) is refrozen to –18°C. The cryoprecipitate thus produced is rich in factor VIII and fibrinogen. It can be used in the treatment of hemophilia A, von Willebrand's disease and congenital hypofibrinogenemia.

Factor VIII and IX concentrates

These concentrates are prepared by fractionating multiple donations of fresh plasma collected from 2,000–5,000 donors. It is heat-treated to reduce the risk of HIV and hepatitis B transmission. It provides 200–300 litres per unit and can be reconstituted in as little as 10 ml of water. The advantage of using this preparation is that it enables administration at home.

Albumin

Albumin is available as salt-poor albumin which contains 200 g/L of albumin and 130 mmol/L of sodium. It is used in the treatment of hypoproteinemia due to gastrointestinal, liver or kidney disease. It is increasingly finding use in total parenteral nutrition units.

Human normal immunoglobulin (HNI)

This is prepared from pools of 1000 normal donations. It is used in the management of hypogammaglobinemia. It is also given prophylactically in patients at risk of developing viral hepatitis.

Human specific immunoglobin

These are fractions prepared from blood with a high content of specific antibody against diseases such as tetanus, hepatitis B and herpes zoster.

Adverse Effects of Transfusions

Hemolytic reactions

Hemolytic reactions due to ABO and Rh incompatibility are relatively rare events due to the precision of cross-matching techniques. Anti-A or anti-B antibodies present in the recipient's blood hemolyse donor RBCs in ABO incompatibility. The two main pathological processes precipitated by a hemolytic transfusion reaction are renal damage and disseminated intravascular coagulation. Management of this crisis is dealt with elsewhere in this chapter.

Delayed hemolytic transfusion reaction

Delayed hemolysis occurs due to an anamnestic antibody response to the transfused red cell antigens in a previously immunised

[1] Cryoprecipitate is not useful in hemophilia B since it does not contain factor IX.

recipient. The allo-antibody is usually of the IgG group. It is not detectable by the direct Coomb's test prior to transfusion. Direct Coomb's test is positive only after the transfusion triggers hemolysis. This uncommon complication is suspected when fever, jaundice and an unexplained fall in hemoglobin develop after a transfusion.

Non-hemolytic transfusion reactions

Fever As has been discussed earlier, patients sensitised to leukocyte antigens develop fever during the transfusion. This complication cannot be differentiated from the more ominous ABO incompatible hemolytic reactions without laboratory support. Hence, the transfusion is discontinued until ABO incompatibility is disproved. Recurrence of this reaction can be prevented by administration of leukocyte-poor blood.

Urticaria When the patient has antibodies to antigens in the donor plasma, urticaria can develop as a complication during the transfusion. Prophylactic antihistamines and washed red cell preparations have reduced the incidence of this reaction.

Anaphylactic transfusion reactions Anaphylaxis to blood products is rare. It is seen to occur in patients who are IgA deficient and who have antibodies to IgA. To prevent reactions in sensitised patients, blood products free of IgA must be transfused.

Infections Acquired immunodeficiency syndrome (AIDS) can be transmitted by whole blood transfer and by factor VIII concentrates. To prevent the risk of HIV transmission, blood donors should be screened. Heat treatment of blood components also helps in reducing the risk of AIDS particularly in patients treated for clotting factor deficiencies.

Viral hepatitis Screening of donors for hepatitis B has reduced the incidence of posttransfusion hepatitis. However, the risk of hepatitis due to non-A and non-B are still high. Serological tests for detecting the latter are not yet widely available thus accounting for the difficulty in preventing this infection. Cytomegalovirus and the malarial parasite can survive in both fresh and stored blood and can be transmitted to the recipient during transfusion Cytomegalovirus infection can cause mild fever, splenomegaly and reactive lymphocytosis in the transfused patient. Paroxysms of fever with chills following a transfusion is suggestive of malaria. Blood should be screened for CMV antibodies and malarial parasite prior to transfusion. Routine testing of blood for syphilis has reduced its occurrence following transfusion.

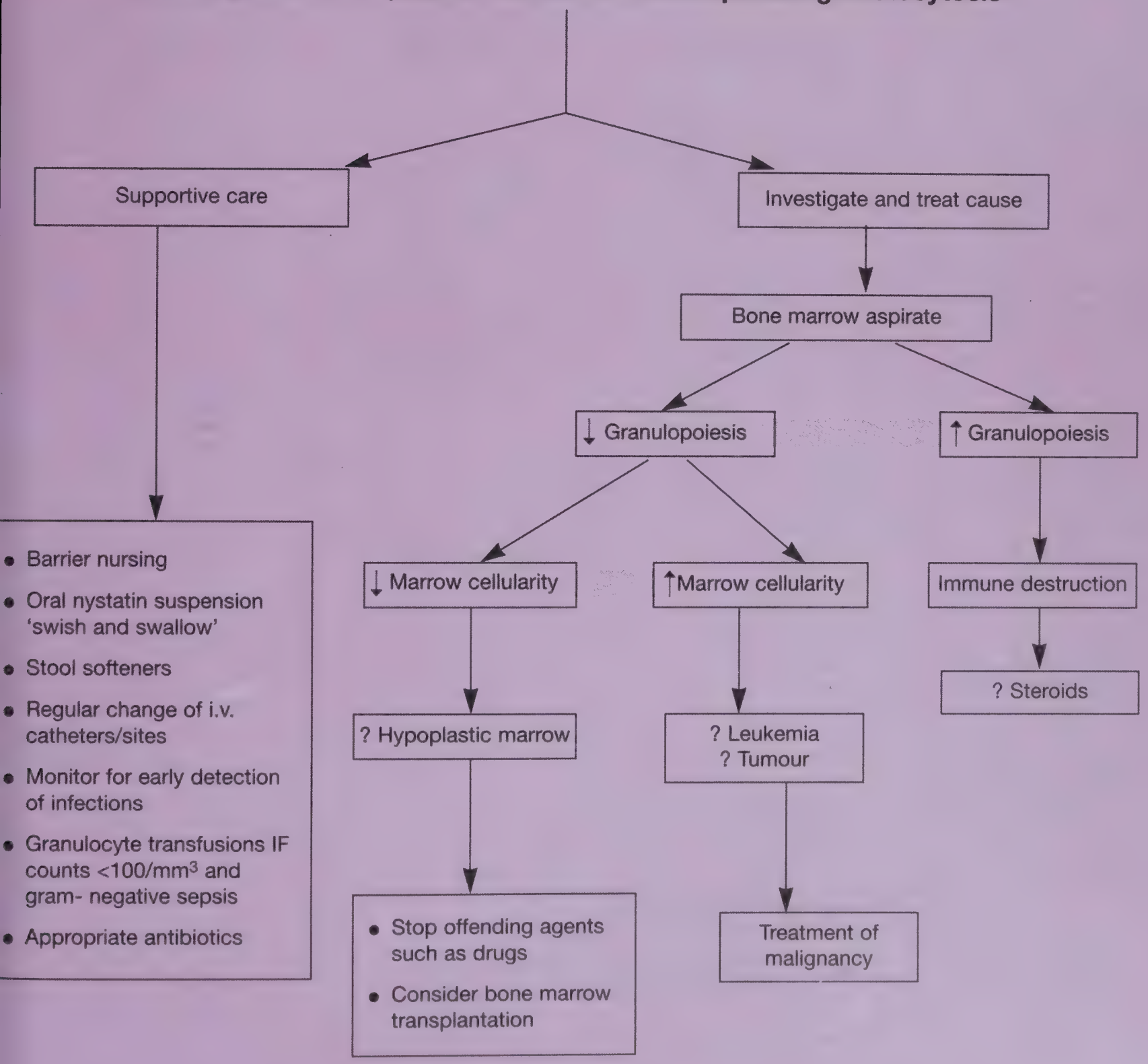
Delayed complications of blood transfusion

Patients receiving recurrent blood transfusions, have an increased iron turnover. Accumulation of excess iron in the heart, liver and endocrine organs can, over a period of time, cause organ dysfuction.

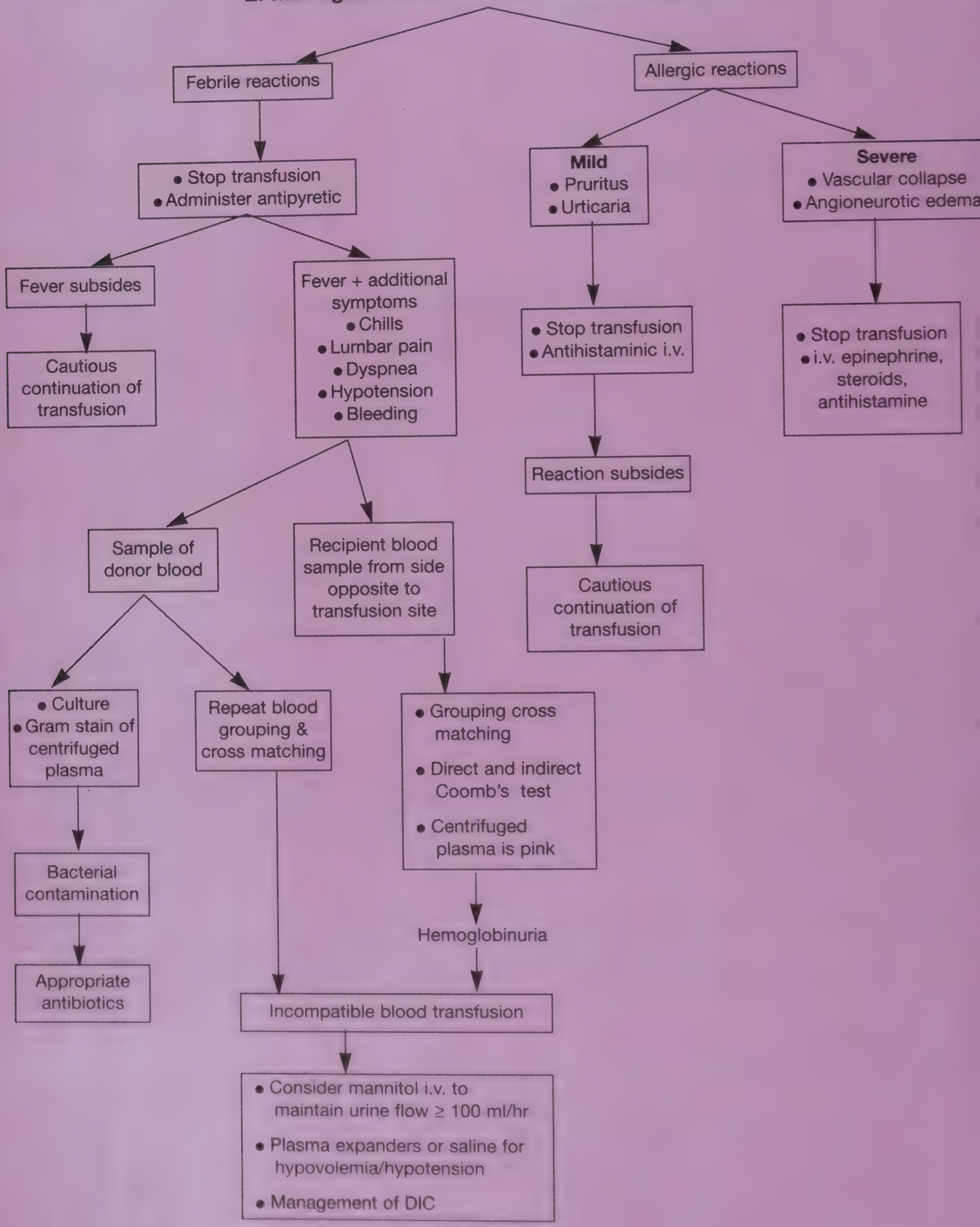
Immunocompetent lymphoid cells from the donor can engraft in immunosuppressed recipients and cause '*graft versus host*' disease. Irradiation of donor blood helps to reduce the risk of this complication.

5.9 Hematologic emergencies

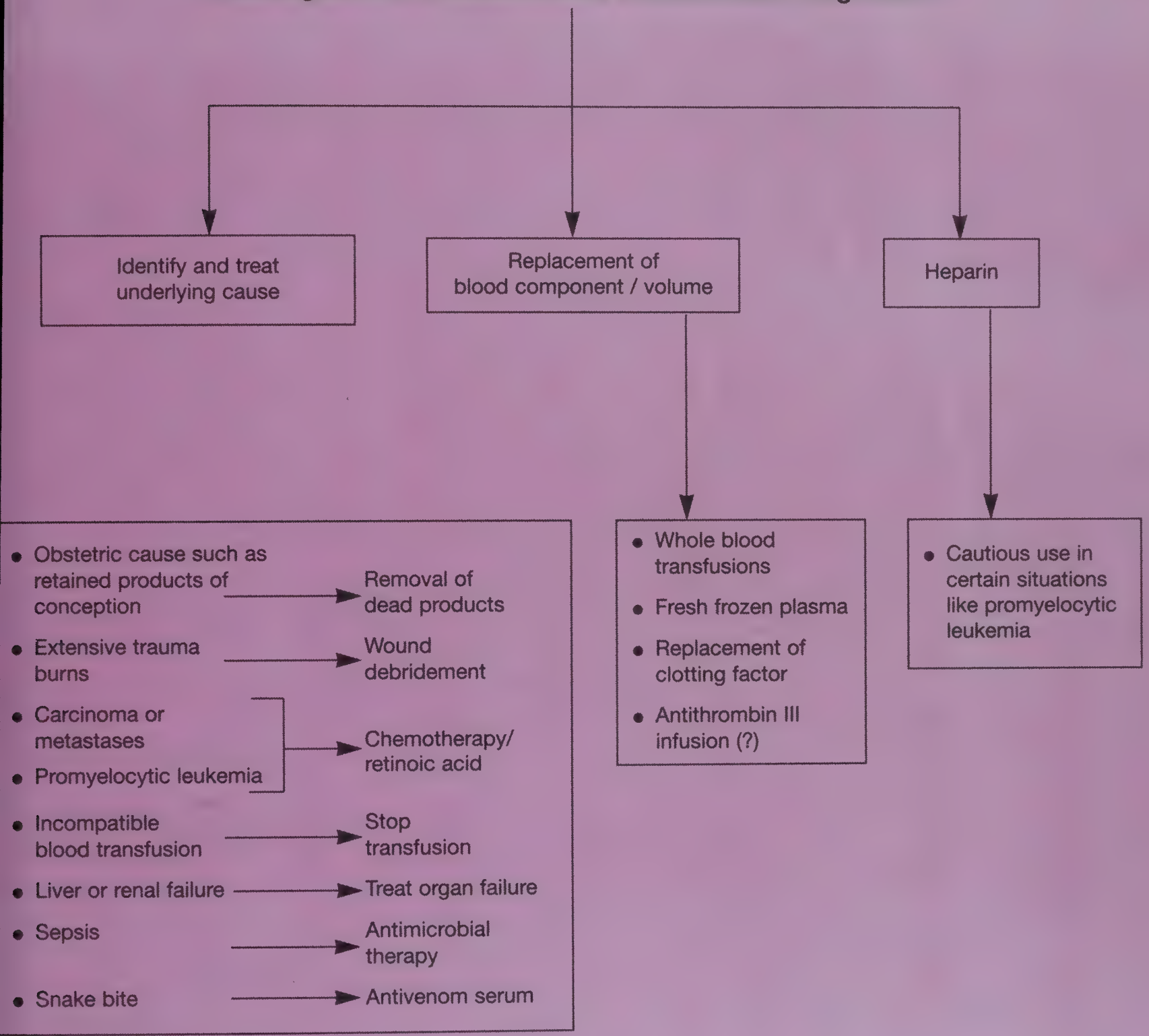
1. Management of a patient with severe neutropenia/agranulocytosis



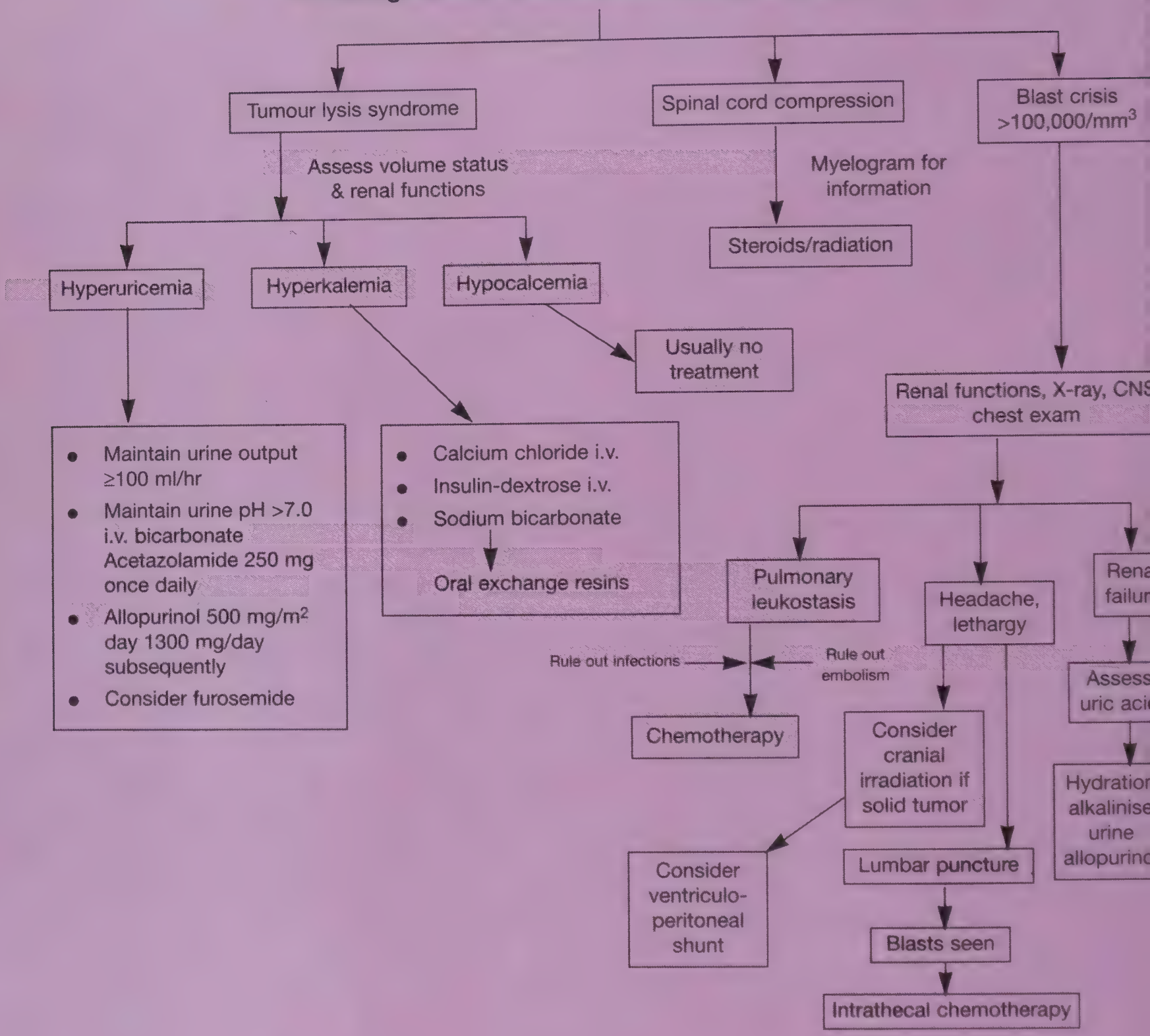
2. Management of blood transfusion reactions



3. Management of disseminated intravascular coagulation



4. Management of hemato-oncologic emergencies



16

Endocrine and Metabolic Disorders

16.1 Principles of endocrinology

Hormones

Hormones were originally defined as chemical agents released from one group of cells which travel through the bloodstream to affect a different group of cells. This definition has been modified and expanded over the years. A hormone is now defined as an *information-transferring molecule* which carries information from one set of cells to another set for the good of the cell population as a whole. This new definition includes molecules which mediate *paracrine* and *autocrine* communication. Paracrine hormones are conveyed over short distances by diffusion through the interstitial space to act on neighbouring cells. An example of a paracrine substance is somatostatin; secretion of somatostatin is stimulated by glucose, glucagon and gut hormones. Autocrine hormones (also called *autacoids*) are substances that are synthesised at (or very close to) their site of action. Prostaglandins are examples of autacoids (Fig 16.1). Hormones differ from vitamins in that they are not incorporated into another molecule and do not serve a nutritive role in responsive tissues.

The three main classes of hormones are steroids, proteins and polypeptides, and amino acid derivatives (catecholamines and thyroid hormones). Table 16.1 provides a comparative overview of these three principal classes of hormones.

Protein and polypeptide hormones are water soluble, and circulate unbound in plasma. These hormones vary a great deal in their size (thyrotropin releasing hormone is a tripeptide, whereas prolactin has 198 amino acid residues). Peptide hormones are often synthesised on the rough endoplasmic reticulum of the manufacturing cell as a *prohormone* (for example, growth hormone) or a *preprohormone* (for example, insulin, parathyroid hormone). These prohormones are then spliced in the Golgi complex, covalently modified and folded (*post-translational modification*) to generate the secretory form of the hormone. An important feature of peptide hormone synthesis is that separate genes may regulate the generation of the prohormone and its subsequent modification. Furthermore, the same prohormone may be metabolised into different hormones in different cells; for instance, pro-opiomelanocortin (POMC) can generate corticotropin, lipotropin, melanotropin and endorphins. Peptide hormones are released into blood by exocytosis. They then circulate to their target cell where they generally bind to cell surface receptors. These peptide hormone receptors have a *hormone binding site* on the outer cell membrane and an activity domain facing the inside of the cell, that is, they tend to be cell membrane-spanning. When the peptide hormone binds its receptor, the latter becomes

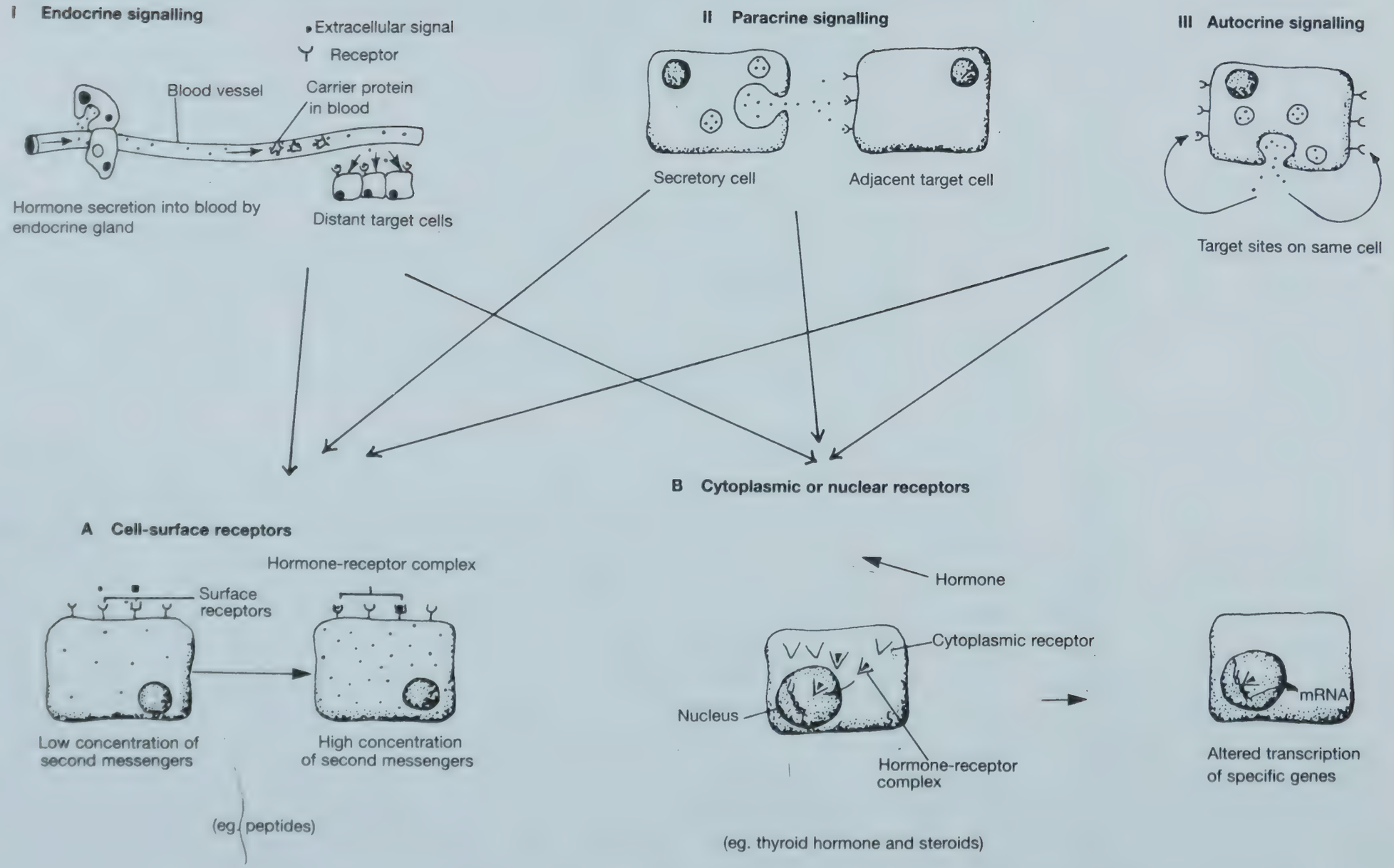


Fig 16.1 The three methods of cell to cell communication and the two mechanisms of action of hormones

Table 16.1 A comparison of the three principal classes of hormones

Feature	*Peptides*	*Steroids*	*Amines*	
			Catecholamines	*Thyroid hormone*
Tissue of origin	Ectoderm (pituitary, hypothalamus) and endoderm (pancreatic islet cells, parathyroid)	Mesoderm (adrenal cortex, testis, ovary)	Neural crest (adrenal medulla)	Endoderm (thyroid gland)
Water solubility	Excellent	Limited	Good	Limited
Storage	Subcellular cytoplasmic granules	None	Cytoplasmic secretory granules	Extracellular (as thyroglobulin)
Plasma binding proteins	Rare	Present	Limited	Present
Site of action on target cells	Plasma membrane	Nucleus	Plasma membrane	Nucleus
Half-life	Short (minutes)	Long (hours)	Very short (seconds)	Very long (hours to days)

ctivated. The activated receptors distribute the nolecular information within the cell with the nelp of intracellular *second messengers*. These econd messengers change the activity of existing cell enzymes. At least 4 types of receptors are ecognised. *R1 receptors* are coupled to cell nembrane *G proteins*. G proteins are neterotrimer molecules which bind to guanine nucleotides GTP and GDP. These G proteins ransduce signals from the hormone membrane eceptor to intracellular enzymes. If the normone receptor is coupled to Gs (stimulatory) proteins, adenylate cyclase is activated and the ntracellular cAMP increases. Examples of normones which stimulate adenylate cyclase nclude ACTH, ADH, calcitonin, gonado-ropins, PTH and TSH. If the hormone receptor s coupled to Gi (inhibitory) proteins, adenylate yclase is inhibited and cAMP levels decrease. Examples of hormones inhibiting adenylate yclase include somatostatin and angiotensin II.

Some other peptide hormone receptors *R2 receptors*) possess intrinsic enzyme activity, hat is, tyrosine kinase activity. Depending on he particular hormone which attaches to it, the yrosine protein kinase receptors give rise to pecific biologic responses. For instance when insulin binds to these receptors, glucose uptake is stimulated, whereas when epidermal growth factor binds to these receptors, cellular proliferation is triggered.

Growth hormone and prolactin are other hormones whose receptors do not have intrinsic tyrosine kinase activity; yet, somehow these hormones activate cytoplasmic tyrosine kinases. The *R3 receptors* stimulate the enzyme guanylate cyclase levels. Examples of hormones which activate guanylate cyclase include the atriopeptins (atrial natriuretic peptides: peptides produced by cardiac atrial tissue and which cause natriuresis, diuresis, vasodilation and inhibition of aldosterone secretion). The *R4 receptors* activate phospholipase C. This results in increased turnover of phosphatidyl inositol within the cell and the production of diacylglycerol and inosine triphosphate (ITP). ITP stimulates increased calcium influx into the cell and stimulates the intracellular calcium-dependent regulatory protein called *calmodulin*. Calmodulin in turn stimulates other protein kinases (CAM-kinases). Thus, in this interaction phosphoinositol products act as secondary messengers while the calcium acts as a tertiary messenger.

Some peptide hormones such as insulin, prolactin, parathyroid hormone and gonadotropins do enter cells. They may do so while they are attached to mobile receptors (human chorionic gonadotropin), or by themselves. The half-life of protein-peptide hormones varies from a few minutes (peptides) to a few hours (glycoprotein hormones). Peptide hormones are inactivated by proteases in the target cells.

Steroid hormones are synthesised from the precursor cholesterol. They are derived from the parent nucleus which has a phenanthrene component (consisting of rings A, B and C) and a hydrogenated cyclopentane ring (D ring).[1] 25-hydroxyvitamin D_3 and 1,25-dihyroxyvitamin D_3 are related compounds called *secosteroids* (which lack the B ring). Steroid hormones are released into circulation by simple diffusion. They are carried in plasma bound to carrier proteins called steroid-binding globulins. The free steroid hormone is in equilibrium with the bound hormone and constitutes a very small proportion of the total hormone. Nevertheless, it is the free hormone which is biologically active and which is important in *feedback regulation* (see below). The free fraction of the steroid hormones enters the target cells and binds to specific mobile receptors in the cytoplasm. All steroid hormone receptors share a common structure which includes two zinc-containing finger-like domains which bind to *recognition elements* on the cellular DNA. These regions of the DNA are also called hormone response elements (HREs). The steroid-receptor complex enters the nucleus and mediates specific messenger RNA synthesis. The half-life of steroid hormones varies from a few minutes (30 minutes for aldosterone) to a few days (15 days for 25-hydroxyvitamin D_3). Steroid hormones are reduced, hydroxylated and conjugated (to glucuronide or sulphate) in the liver and excreted in the bile.

The third class of hormones are derivatives of the amino acid tyrosine. This class includes the water soluble catecholamines and the lipi soluble thyroid hormones. Catecholamines ar secreted into the circulation by exocytos of the chromaffin granules in which they ar stored. They circulate either in a free form or a conjugates (sulphate or glucuronide). Catech lamines exert their effect through plasm membrane receptors. The hormone-recept interaction results in activation of the secon messenger (usually adenylate cyclase) which turn activates target protein kinases that media the effects. Catecholamines have a very sho half-life of 10–15 seconds.

The thyroid hormone is secreted by diffusio into the bloodstream where it circulates boun to thyroxine-binding globulin. The free hormon enters the target cells and combines with nucle receptors. The hormone-receptor complex the binds to specific DNA sequences to initia transcription and translation. The half-life is (triiodothyronine) to 7 days (thyroxine Thyroid hormones are deiodinated, deaminate and deconjugated by the liver.

Integration of Endocrine Responses

Concept of feedback loops

The production of most hormones is regulate directly or indirectly, by its very own metabo activity. This phenomenon is termed *feedba* and is accomplished through *positive* an *negative feedback loops*. Thus, hormon produced in response to pituitary troph hormones (such as cortisol) exert feedback the hypothalamic-pituitary axis to regulate the own levels. In reality, the process is complicat as shown in Fig 16.2. The presence of the feedback loops has two important clinic implications:

a. Whenever endocrine function is assessed, it essential to estimate both the hormone and t end product (paired tests) simultaneously. F instance, in order to interpret a low thyroxi level, it is necessary to evaluate thyro stimulating hormone (TSH) which is secreted the pituitary. A low thyroxine with a low TS

[1] Hence called *cyclopentanoperhydrophenanthrene* nucleus

suggests a primary pituitary pathology. On the other hand, a low thyroxine with high TSH suggests a primary thyroid disorder. When both pairs (thyroxine and TSH) are elevated together, it is important to assess for the presence of clinical evidence of hormone hyperactivity. If there is no clinical evidence of hormone excess, but levels of the pair are elevated, *end-organ resistance* is likely. When both pairs are elevated and there is clinical evidence of hyperfunction, an *autonomy* of production, that is, relative freedom from feedback, is suggested. This is typically seen with ectopic production of hormones by a trophic hormone secreting tumour.

b. The other important implication of feedback is that it helps us fomulate *stimulation* and *suppression tests* for assessment of hormone functions.

Coordinate Endocrine Responses

Normal bodily response to usual and unusual forms of stimuli often requires the concerted participation of several diverse hormones, each regulated by different influences. It is amazing that despite this apparent diversity in hormones and their regulation, they interact in a coordinated fashion in response to various stimuli. A classic examples is the body response to fasting. Fasting is associated with a diminution in blood glucose levels. Initially, the body maintains blood glucose levels in the low normal range by drawing on its glycogen stores. This *glycogenolysis* (breakdown of glycogen into glucose derivatives) is brought about by the combined action of glucagon and epinephrine, both of which are released in response to falling blood glucose levels. If fasting continues uninterrupted, the body turns to cortisol-mediated *gluconeogenesis* (formation of glucose from non-carbohydrate precursors, such as pyruvate, glycerol and certain amino acids). Other hormone systems also help in this coordinate response. Insulin secretion is inhibited, and the peripheral conversion of thyroxine to its more active metabolite triiodothyronine (explained later in the thyroid gland section) is also inhibited; the latter step serves to reduce peripheral metabolic demands which is important for glucose conservation. Body responses to 'fright' are also similarly coordinated with the complex interplay of several hormones to achieve one important end: coping with the stressful situation presented.

Cyclicity

Hormone secretion is often periodic or rhythmic. This cyclicity of release may vary over a period of minutes to hours (*ultradian*), over 24 hours (*circadian*) or over longer periods. An example of circadian variation is that of adrenocorticotrophic hormone (ACTH) and its pair, cortisol. Another example is the variation of LH and FSH release over the time course of a menstrual cycle. This in turn is related to the pulsatile release of the hypothalamic releasing hormones (in this case LHRH). Knowledge of such variation is critical in evaluation of blood levels of hormones. Thus, plasma cortisol levels should be interpreted as high, low or normal only if the exact timing of the sample is known. Similarly, evaluation of endometrial cytology depends on the phase of the menstrual cycle in which it is obtained.

Hormonal Aberrations in Endocrinopathies

Generally speaking, endocrine disorders arise due to one of three pathogenetic mechanisms: hormone *deficiency,* hormone *excess* or hormone *resistance*.

Hormone deficiency is probably the most common mechanism for endocrine disorders. A deficiency may arise due to genetic defects in biosynthetic enzymes (congenital adrenal hyperplasia) or as a result of destruction of the glands by infection (tuberculosis causing Addison's disease), immunoinflammation (Hashimoto's thyroiditis), neoplasms (pituitary adenoma), or infarction (postpartum pituitary necrosis).

The *long-loop feedback* (1) is the effect of the target gland hormone on the hypothalamus.
The *short-loop feedback* (2) is the effect of the pituitary hormone on the hypothalamus or of the target gland hormone on the pituitary gland. The *ultrashort-loop feedback* (3) is the effect of the hypothalamic releasing hormone on the hypothalmus or of the pituitary hormone on the pituitary gland or of the target gland hormone on the target. Plus signs indicate stimulation and minus signs indicate negative feedback.

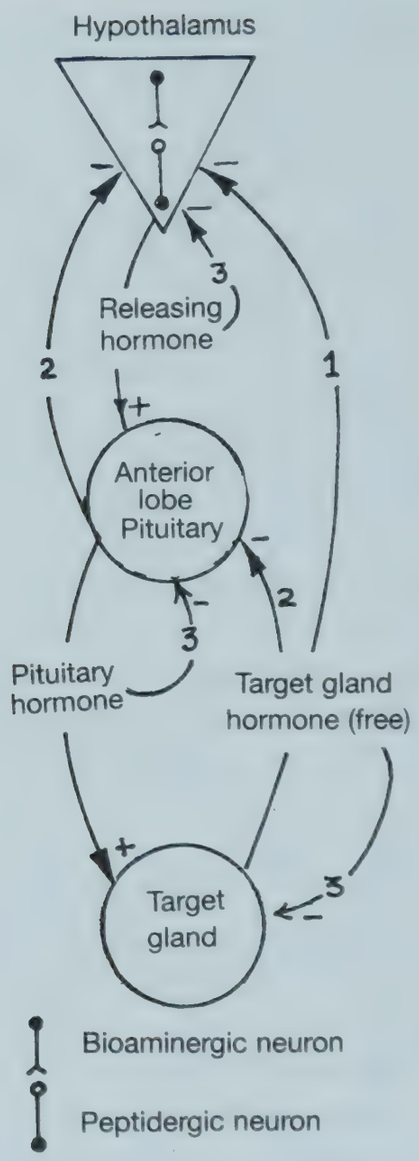


Fig 16.2 Feedback control of hormone secretion

Hormone excess states arise from increased production of hormones in the gland, or at ectopic sites due to neoplasms (Cushing syndrome), increased production due to autoimmunity (antireceptor antibodies act as agonists as in Graves disease), due to an enhanced peripheral conversion of the hormone precursors (in liver disease androstenedione is diverted towards estrogen production in the periphery), or as a consequence of iatrogenic administration (corticosteroids).

Hormone resistance states may be due to defects in hormone receptors (vitamin D-resistant rickets) or defects in postreceptor signalling mechanisms (pseudohypoparathyroidism). Clinical signs of hormone deficiency are seen in the presence of high levels of the hormone and hyperplasia of the concerned gland (due to a lack of feedback inhibition).

Endogenous Opioid Peptides

Opioid peptides are a group of endogenous compounds which bind to morphine receptors within the central nervous system. Three classes of such peptides are recognised: the *endorphins*, the *dynorphins* and the *enkephalins*.

The *endorphins* are peptides derived from β-lipotropic hormone (β-LPH) which in turn arises from a precursor compound called *proopiomelanocortin* (POMC). POMC is also the precursor of ACTH. β-endorphin arises from proteolytic cleavage of β-LPH (amino acid

residues 61–91). β-endorphin is cleaved into α-endorphin (amino acid residues 61-77). α-endorphin forms γ-endorphin (amino acid residues 61-76). The endorphin system within the central nervous system is characterised by long fibre projection systems extending from the ventral hypothalamus (arcuate nucleus) to the periventricular area. Endorphins are also found in fibres of other neurons projecting into the mesencephalic periaqueductal grey. β-endorphin is the principal endorphin; besides the regions described above, it is also produced in the anterior pituitary. It binds to opiate receptors to cause analgesia, sedation, respiratory depression and modulate functions of the limbic system (drive for water, food and sex).

The *dynorphins* arise from a separate precursor substance (sometimes called *proenkephalin B*). Their highest concentration is in the hypothalamus, brainstem and spinal cord. Dynorphins are involved in several neuromodulatory roles (pain transmission, motor system, sympathetic tone, limbic system and cortical functions), which include regulation of arginine-vasopressin secretion in the posterior pituitary.

The *enkephalins* are pentapeptides whose precursor compound is *proenkephalin* A. Two types, *met-* and *leu-enkephalin,* are well-recognised. Enkephalins have the widest distribution within the nervous system. They are found in the basal ganglia, limbic structures, and the spinal cord (dorsal grey matter and the substantia gelatinosa). Enkephalins mediate analgesia (central periaqueductal receptors and suppression of substance P in the spinal dorsal grey matter), participate in emesis and antitussive actions (vagal nucleus) and visceral reflexes including respiration (nucleus tractus solitarius in brainstem).

16.2 Approach to a patient with endocrine problems

Approach to a Patient with Growth Retardation

Growth retardation is considered to be present in a child or an adolescent whose height is three standard deviations below the normal mean for that age, or below the third percentile on standard growth charts.

Etiopathogenesis Normal body growth depends on the adequate provision of nutrients, normal function of the endocrine system and normal tissue responses. Between the ages of 2–12 years, children grow at an average rate of 5 cm per year. This growth rate is doubled during puberty and is termed the *adolescent growth spurt*; in girls the spurt occurs between 10 and 14 years (average of 12 years), and in boys it occurs between 12 and 16 years (average of 14 years). Several hormones play an important role in normal growth. The growth hormone is essential for linear growth and exerts its effects principally on the epiphyseal plates. It has a lesser effect on epiphyseal maturation and fusion and is not involved in the adolescent growth spurt. The actions of the growth hormone on bone and cartilage are mediated by a family of low molecular weight polypeptides which are generated in the liver and are known as the *somatomedins*. The thyroid hormones are essential for skeletal maturation; they potentiate the skeletal effects of growth hormone, influence linear growth to a lesser extent and play a minor role in the adolescent growth spurt. Androgens are responsible for the growth spurt at puberty in men and women. Testosterone stimulates skeletal maturation, potentiates the effect of growth hormone on epiphyseal cartilage width but does not effect linear growth. Thus, deficiency of any of these hormones can affect growth.

Clinical approach A careful elicitation of history is essential to exclude any chronic disease of the major organ systems. A nutrition history is of importance to exclude growth stunting arising as a consequence of malnutrition. Knowledge of birth weight and early growth, and observation of yearly height increments on growth charts (if available) give valuable clues to the velocity of growth over time. A history of similar problems in siblings or in the parents may suggest either *familial short stature* or a *constitutional delay of growth*. Visual impairment, symptoms of increased intracranial pressure, or a history of polyuria-polydipsia may suggest a pituitary or hypothalamic tumour. A history of constipation, cold intolerance and mental retardation may suggest hypothyroidism. The combined presence of symptoms of hypothyroidism and adrenal insufficiency (asthenia, salt craving) raises the possibility of hypopituitarism. The various causes of growth retardation are listed in Table 16.2. Clinical examination is crucial to ascertain the presence or absence of normal pubertal development. Presence of normal pubertal development suggests familial short stature. If the height is short and puberty is delayed, several possibilities arise and these are depicted in Fig 16.3.

Approach to a Patient with Weight Loss

change of body weight of five per cent or ore, in the absence of dieting measures, is garded as significant weight loss. This refers to e measurement of weight under similar control nditions – not on different scales or wearing fferent clothes.

Etiology The causes of weight loss are listed in Table 16.3. Sudden weight loss over a period of days usually represents the effect of an acute illness such as diarrhea or acute infections. However, it may be physiological in some women who may lose upto a kilogram or more with the menstrual cycle. A similar weight loss due to loss of tissue fluid in the postpartum

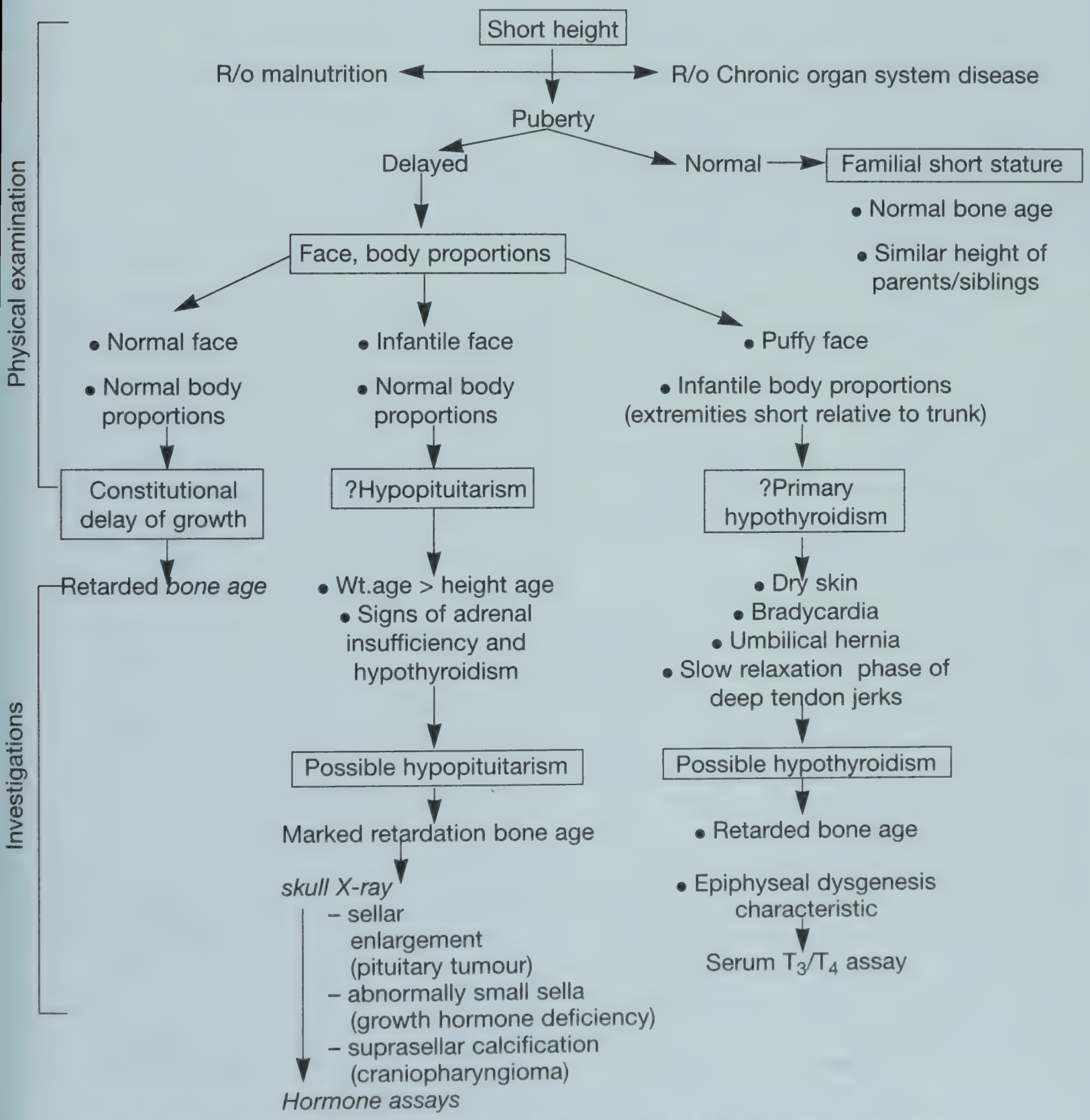


Fig 16.3 Clinical examination and laboratory investigations in a subject with growth retardation

Table 16.2 Causes of growth retardation

1. Apparent underlying condition
   - Malnutrition
   - Chronic infection
   - Chronic renal disease
   - Chronic liver/intestinal disease
   - Congenital heart disease
   - Chronic respiratory disease
2. Familial short stature
3. Constitutional delay of growth
4. Endocrine causes
   - Hypopituitarism
   - Primary hypothyroidism
   - Diabetes mellitus
5. Miscellaneous
   - Inborn errors of metabolism
   - Chromosomal disorders
   - Steroid therapy

period is to be regarded as normal. Weight loss in extreme old age is related to tissue shrinkage and may be physiological. Usually, weight loss is secondary to one of three principal mechanisms:
a. a decreased appetite;
b. accelerated tissue metabolism, usually associated with an increased appetite; and
c. increased loss of calories, usually from the gastrointestinal tract.

Approach A careful clinical history is essential to assess the validity of weight loss. This includes examining actual weight records and seeking evidence in the form of loose clothes, belts or footwear. The time course and extent of weight loss must be established. This should be followed by specific questions on appetite and the daily intake of food. Questions directed towards specific illnesses must be asked. A history of polyuria, polydipsia or delayed healing of skin wounds may direct attention to the possibility of diabetes mellitus. A history of heat intolerance, palpitations, excessive perspiration and diarrhea may suggest thyrotoxicosis. A history of chronic diarrhea or steatorrhea may suggest the possibility of a malabsorption syndrome. A history of night sweats, fever, cough raises the possibility of tuberculosis. A history of letharg nocturia, anorexia, nausea or hiccups may lea the physician to suspect chronic renal disease the likely cause of weight loss. Loss of libid amenorrhea, visual symptoms may sugge endocrine disorders such as panhypopituitaris A history of lymph node enlargement, change bowel habits or bleeding from any mucosal tra may indicate tuberculosis, or a hematologic gastrointestinal neoplasm. The personal histo must be detailed, especially regarding t likelihood of a depressive disorder which c present as weight loss.

The physical examination and the subseque investigations in a patient with weight loss a displayed in Figs 16.4 and 16.5.

Table 16.3 Causes of weight loss

A. With increased appetite
- Thyrotoxicosis
- Diabetes mellitus
- Some fevers
- Pheochromocytoma
- Exertion

B. With diminished appetite
- Depression
- Anorexia nervosa
- Drug intake (illegal and medicational)
- Subacute and chronic infections (such as tuberculosis)
- Gastrointestinal disorders
  - Peptic ulcer disease
  - Obstruction of the gastrointestinal tract
  - Chronic renal failure
- Advanced congestive heart failure
- Chronic respiratory failure
- Addison's disease
- Chronic alcoholism
- Chronic immunoinflammatory disease
- Malignant disease anywhere

C. With normal appetite
- Malabsorption syndrome
- Loss of muscle mass
- Motor neuron disease
- Myopathies
- Panhypopituitarism

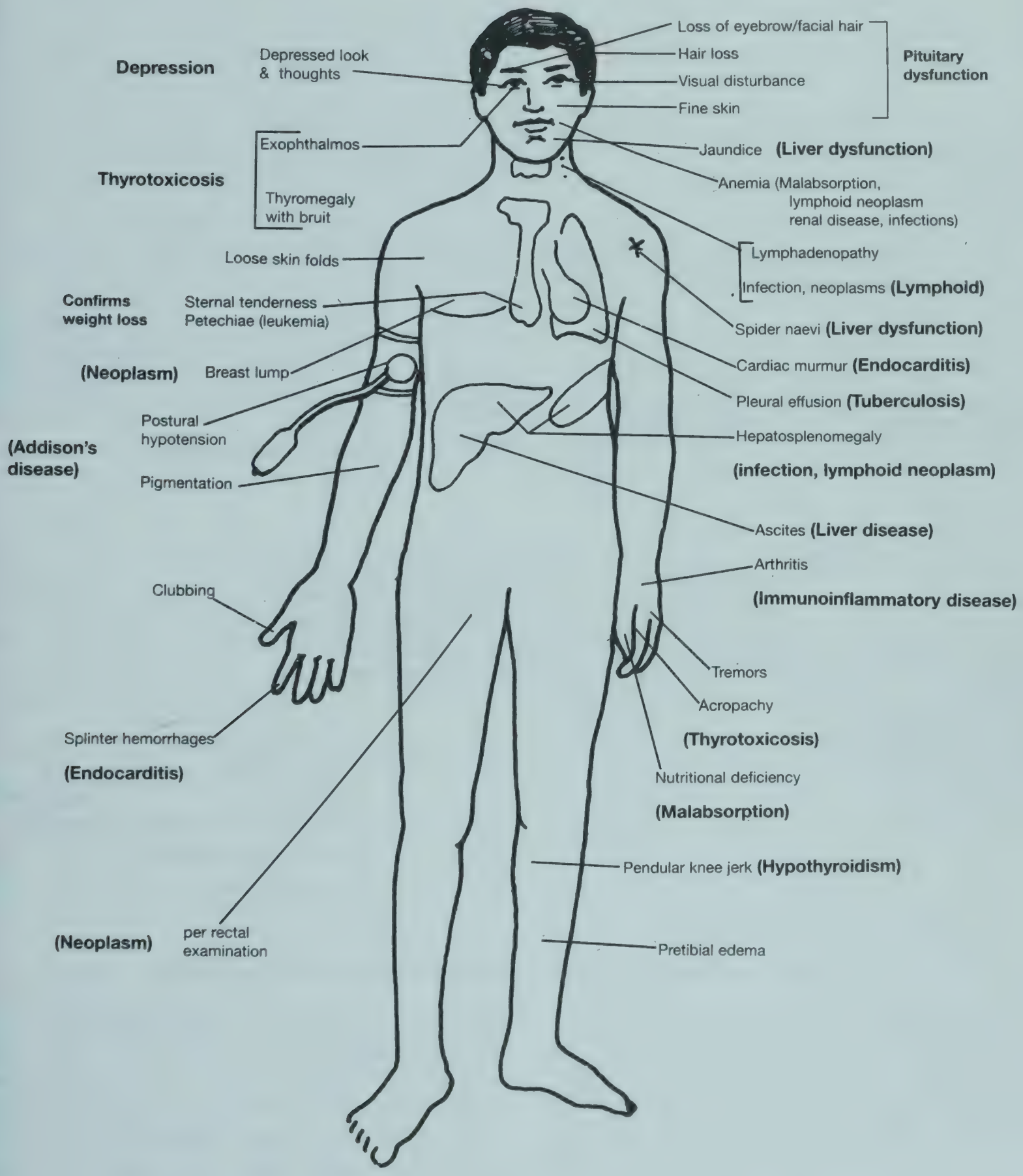


Fig 16.4 Clues to the etiology of weight loss on physical examination

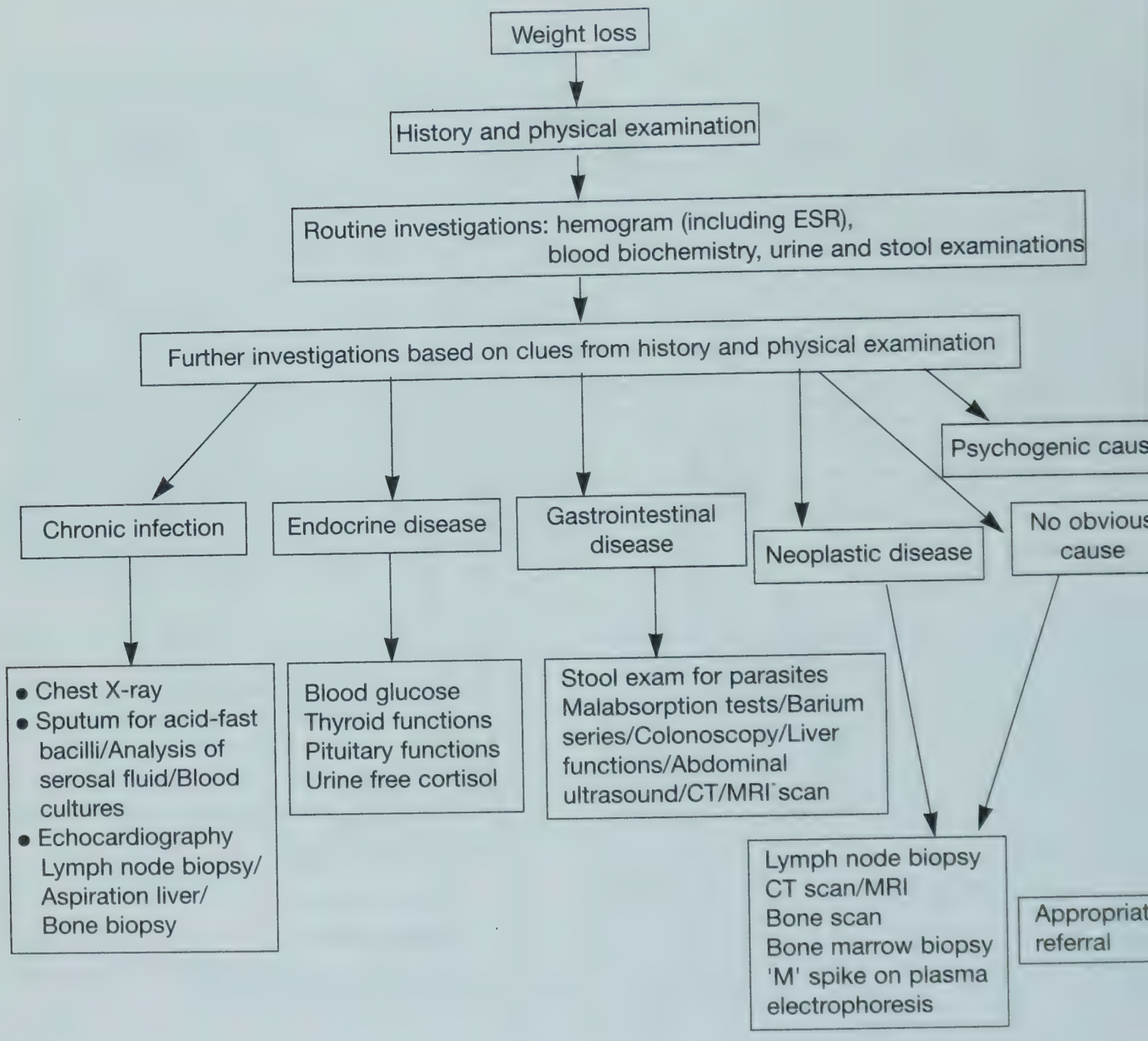


Fig 16.5 Approach to diagnosis and investigations in a patient with weight loss

Approach to a Patient with Hirsutism

Hirsutism refers to excessive hair growth in women in the hormone-dependent areas of skin such as face, chest, axillae and pubis. Hirsutism must be distinguished from *hypertrichosis*, which represents excess growth of hair on the head, back and extremities.

Etiopathophysiology The major circulating androgens in women are (in decreasing order of potency) testosterone, androstenedione a dehydroepiandrosterone (DHEA). The ma source of DHEA is the adrenal glan Approximately 50 per cent of androstenedio is secreted by the adrenal glands and the rest the ovarian theca cells and stroma. The ma sources of testosterone are the periphe conversion[1] of adrenal androgens (50%), dir

[1] This conversion occurs in the liver, skin, blood a skeletal muscle.

Table 16.4 Causes of hirsutism

1. Idiopathic (50%)
2. Ovarian causes
   - Polycystic ovarian disease
   - Ovarian tumours secreting excess androgen
3. Adrenal causes
   - Cushing syndrome
   - Congenital adrenal hyperplasia (adult/late onset)
   - Adrenal tumours
4. Drugs
   - Androgens
   - Corticosteroids
   - Minoxidil
   - Diazoxide
   - Phenytoin

secretion from the adrenals (30%) and the ovaries (20%). Hirsutism is the result of androgen excess of ovarian or adrenal origin. When plasma testosterone levels are normal, it is very likely that testosterone production is still increased but is associated with increased extrahepatic clearance. The causes of hirsutism are enumerated in Table 16.4.

Clinical approach The first decision the clinician has to take is whether or not hair growth is excessive. It must be remembered that racial factors play a role in normal hair growth; hair in the moustache region may be normal in some races but unusual in someone from the states in northeast India. Once excess hair growth is diagnosed, a careful drug history is essential to exclude iatrogenic hirsutism. A family history of a similar disorder is important as it may either indicate a familial trait or a familial disorder such as polycystic ovarian disease. The presence of associated history of *virilisation* is important as it may be a marker of ovarian or adrenal tumours.[1] The features of virilisation include a history of clitoromegaly and deepening of voice. Virilisation is usually associated with symptoms of *defeminisation*, such as male pattern baldness, breast atrophy, amenorrhea and an alteration of the female body habitus.

Physical examination also yields valuable clues to the etiology of hirsutism. Presence of generalised obesity, acne and a modest degree of hirsutism is common in idiopathic hirsutism, polycystic ovary disease and adult onset congenital adrenal hyperplasia. Presence of truncal obesity, cutaneous striae or ecchymoses, plethoric facies with or without hypertension may be clues to an underlying Cushing syndrome. A careful pelvic examination may detect unilateral (tumour) or bilateral (polycystic ovary disease) ovarian enlargement.

The laboratory work-up of a subject with hirsutism is indicated in Fig 16.6.

Management

The appropriate treatment of hirsutism depends on its cause and extent. Mild idiopathic hirsutism needs only patient reassurance. Moderate degree of idiopathic hirsutism can be treated with either medroxyprogesterone or an oral contraceptive. A severe degree of hirsutism may require electrolysis for cosmetic purposes. Antiandrogens have also been used for treatment of idiopathic hirsutism. The most promising agent is spironolactone given in daily doses of 50–200 mg. Spironolactone inhibits ovarian steroidogenesis, increases peripheral conversion of testosterone to estradiol and competes for the androgen receptor on the hair follicle. Ovarian hyperandrogenism is best treated with a combination oral contraceptive.

Approach to a Patient with Gynecomastia

Gynecomastia is defined as any palpable breast tissue in a male. Any process which causes

[1] Virilisation is rare in idiopathic hirsutism and polycystic ovary disease. It is more common in ovarian tumours as compared to adrenal tumours.

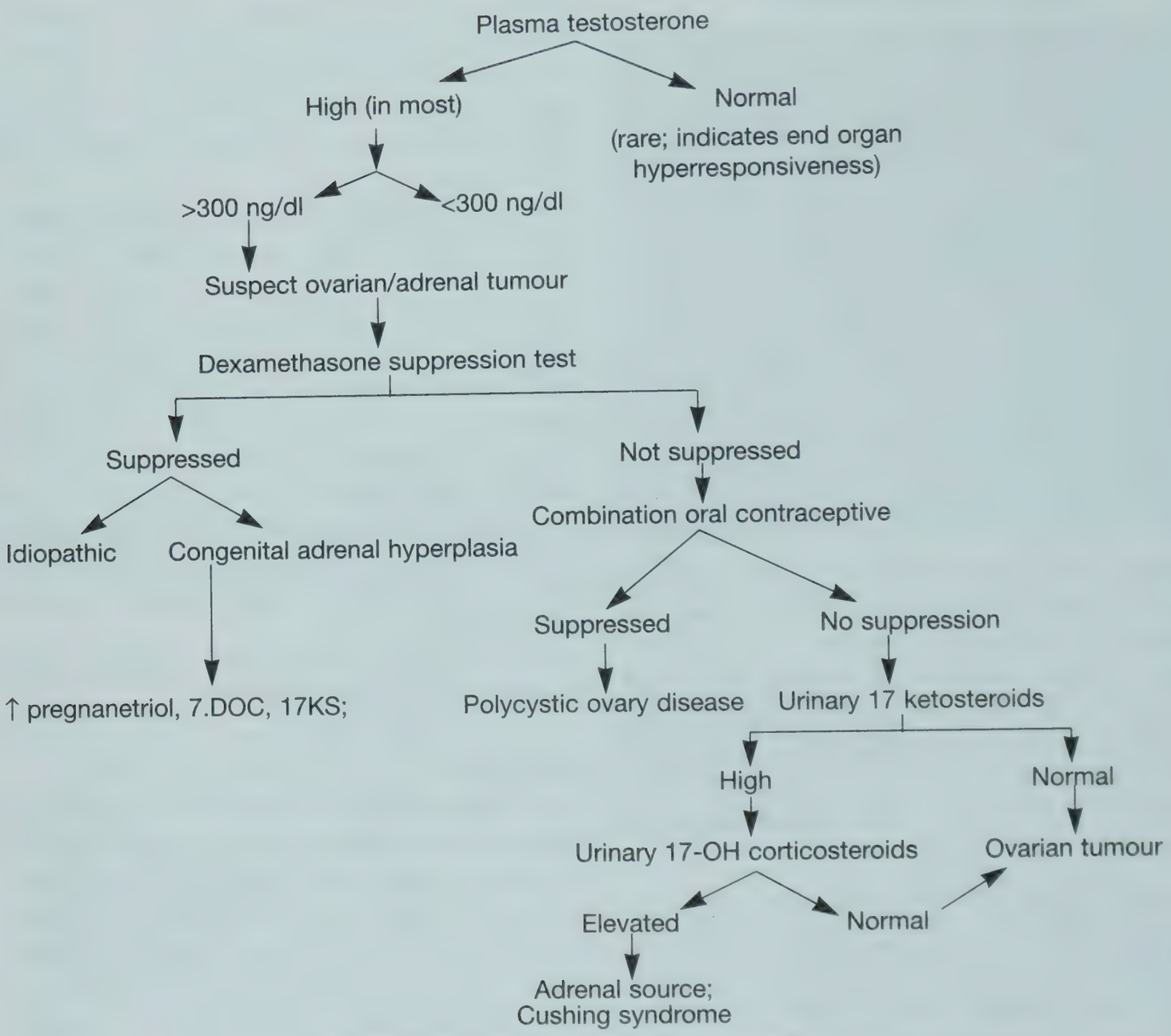


Fig 16.6 Laboratory work-up of a subject with hirsutism

bilateral gynecomastia may also cause unilateral breast enlargement. Gynecomastia is a common problem, and in one study upto 70 per cent of hospitalised men were noted to have palpable breast tissue. It is of clinical importance due to its psychological effects, as well as the fact that it may provide a clue to an underlying disorder. Gynecomastia may occur physiologically during the neonatal period, during puberty, and in old age. It may also occur due to various underlying disorders (Table 16.5).

Table 16.5 Causes of gynecomastia

Physiologic
Neonatal
Pubertal
Involutional (old age)
Pathologic
Hypogonadism
Androgen resistance syndromes
Estrogen-secreting testicular or adrenal tumours
Carcinoma of the lung or other tumours secreting HCG
Liver disease
Thyrotoxicosis
Drugs
Idiopathic

Pathophysiology Gynecomastia may be caused by any process which increases the normal ratio of estrogens to androgens in males. Neonatal gynecomastia is due to placental and maternal estrogens; adolescent gynecomastia is due to transient elevations of estradiol prior to the completion of puberty, and involutional gynecomastia is due to increased extraglandular conversion of androgens to estrogens. Most estradiol and estrone in men is formed in the adipose tissue by the actions of the enzyme aromatase on circulating androgens. Elderly men have a higher proportion of body fat than younger individuals. Therefore, they have a higher estrogen production rate than young men.

Any disorder which decreases testosterone production or action may cause gynecomastia. This is the cause of the gynecomastia seen in primary testicular failure, as well as in secondary testicular failure due to hypothalamic-pituitary insufficiency. Defective testosterone action is seen in the syndromes of androgen resistance. Disorders which increase estrogen secretion or production will also cause gynecomastia. Increased secretion of estrogens may be due to estrogen producing tumours of the testes, such as Sertoli or Leydig cell tumours. Estrogen secretion is also increased as a result of any disorder which elevates plasma gonadotropins, (such as various testicular tumours or bronchogenic carcinomas). Increased production of androstenedione in congenital adrenal hyperplasia, thyrotoxicosis or adrenal cancers will lead to increased substrate availability for estrogen formation in adipose tissue. Decreased catabolism of androstenedione in chronic liver disease may cause gynecomastia by the same mechanism.

Many drugs may cause gynecomastia by several different mechanisms. Various estrogenic substances such as diethylstilboesterol used to treat prostate cancer or digitalis may cause gynecomastia by directly stimulating estrogen receptors. Other drugs such as alkylating agents or ketoconazole may directly inhibit testosterone secretion. Spironolactone, flutamide and cimetidine block androgen receptors. Several other drugs such as marijuana, heroin and methyldopa cause gynecomastia by mechanisms which are as yet poorly defined.

Clinical evaluation It is critical to take a comprehensive drug history (marijuana, heroin, alcohol, etc.) and medication history when evaluating a patient with gynecomastia. Questions relating to male sexual function (impotence or decreased sex drive) are also relevant. Gynecomastia must be differentiated from *lipomastia* on physical examination. This is most easily accomplished by having the patient lie down with his hands behind his head. The examiner then attempts to palpate breast tissue which will feel rubbery or firm. This may be done by placing the thumb and forefinger at opposite margins of the breast. The fingers are then brought slowly together along the nipple line. Enlarged glandular tissue should be concentric to and beneath the areolar area. This must be differentiated from breast carcinoma which will present as a hard mass eccentric to the areola. The remainder of the examination should focus on signs of feminisation (smooth skin on face with telangiectasia), signs of chronic liver disease, hypogonadism, or hyperthyroidism. In a pubertal boy with gynecomastia, it is particularly important to examine the testes for evidence of an estrogen or HCG-secreting tumour.

Because gynecomastia is so common, it is reasonable to defer a work-up if breast tissue is less than 4 cm in size and the breasts are not tender (tenderness would indicate recent growth). If the individual is taking a potentially offending drug, the drug should be discontinued if possible and the patient reevaluated in 1–2 months. If a pathologic cause of the gynecomastia is suspected, the work-up would include serum testosterone, estradiol, HCG, liver function tests, and TSH. However, the cause for gynecomastia is frequently not found

even after an exhaustive work-up. The most common diagnoses of patients referred for breast enlargement are idiopathic gynecomastia and persistent adolescent gynecomastia.

Therapy The vast majority of patients with gynecomastia do not require therapy for the problem. Adolescent gynecomastia should disappear within a few years. Gynecomastia due to drugs or an underlying disorder should regress once the offending agent has been withdrawn or after the disease has been treated. For those individuals who require immediate therapy of their gynecomastia due to psychological reasons, surgical reduction is a reasonable option. Medical therapy using the antiestrogen tamoxifen may also be effective.

Approach to a Patient with Amenorrhea

Amenorrhea is defined as the absence of menstruation in a woman above 16 years of age (that is, the absence of menarche or *primary amenorrhea*), or in any woman of child-bearing age with a history of prior menstruation (*secondary amenorrhea*). Normal menstruation depends on an intact pituitary and hypothalamus (which secrete gonadotropins and their releasing hormones), intact ovaries which respond to the gonadotropins with estrogen and progesterone production, a uterus which is responsive to the estrogen and progesterone stimulation, and a normal patent uterine and vaginal outlet. Disturbances involving any of these anatomical and physiologic components can result in amenorrhea. A good history and physical examination can lead to a diagnosis of the etiology of amenorrhea in most cases, with laboratory testing being required for confirmation only.

History and physical examination

Primary amenorrhea: When faced with a girl of pubertal age who has primary amenorrhea, the physician must first and foremost exclude congenital abnormalities of the uterovaginal outlet and ovarian dysgenesis. Examination for secondary sex characters (notably breast development) and for the presence of a uterus are important initial steps. If *breasts are underdeveloped and a normal uterus is present,* a history of anosmia is sought, height is noted, and plasma gonadotropins are estimated. *Constitutional delay* in onset of puberty is an important cause of primary amenorrhea. In a short female with widely spaced nipples (*shield chest*), a webbed neck suggests the possibility of gonadal dysgenesis (*Turner syndrome*); gonadotropins are typically elevated. Absence of a Barr body is a simple confirmatory test in individuals with classic features. If hirsutism or signs of masculinisation are present, karyotyping is necessary to exclude the presence of a Y chromosome; this is important as the presence of a Y chromosome would necessitate a consideration for gonadectomy to obviate malignant potential. If anosmia is present and eunuchoid features are prominent, *Kallman syndrome* is the likely diagnosis; gonadotropin levels are low. *If breasts are well developed but the uterus is absent,* serum testosterone levels are estimated. In *congenital absence of the uterus,* testosterone levels are low (in the 'female' range). If testosterone levels are in the 'male' range, a karyotype is obtained; presence of an XY karyotype suggests *testicular feminisation syndrome.* If *both breast development and a normal uterus are present, pregnancy* should be excluded and other causes discussed below under secondary amenorrhea must be considered.

Secondary amenorrhea: The first step in the investigation is to exclude *pregnancy.* If pregnancy has been excluded, serum prolactin and gonadotropins should be estimated and a *progesterone withdrawal test* performed (Fig 16.7). Patients with a functioning hypothalamic-pituitary axis and an intact outflow tract should have 'withdrawal' bleeding after administration of progesterone. If there is bleeding, chronic anovulation due to *polycystic*

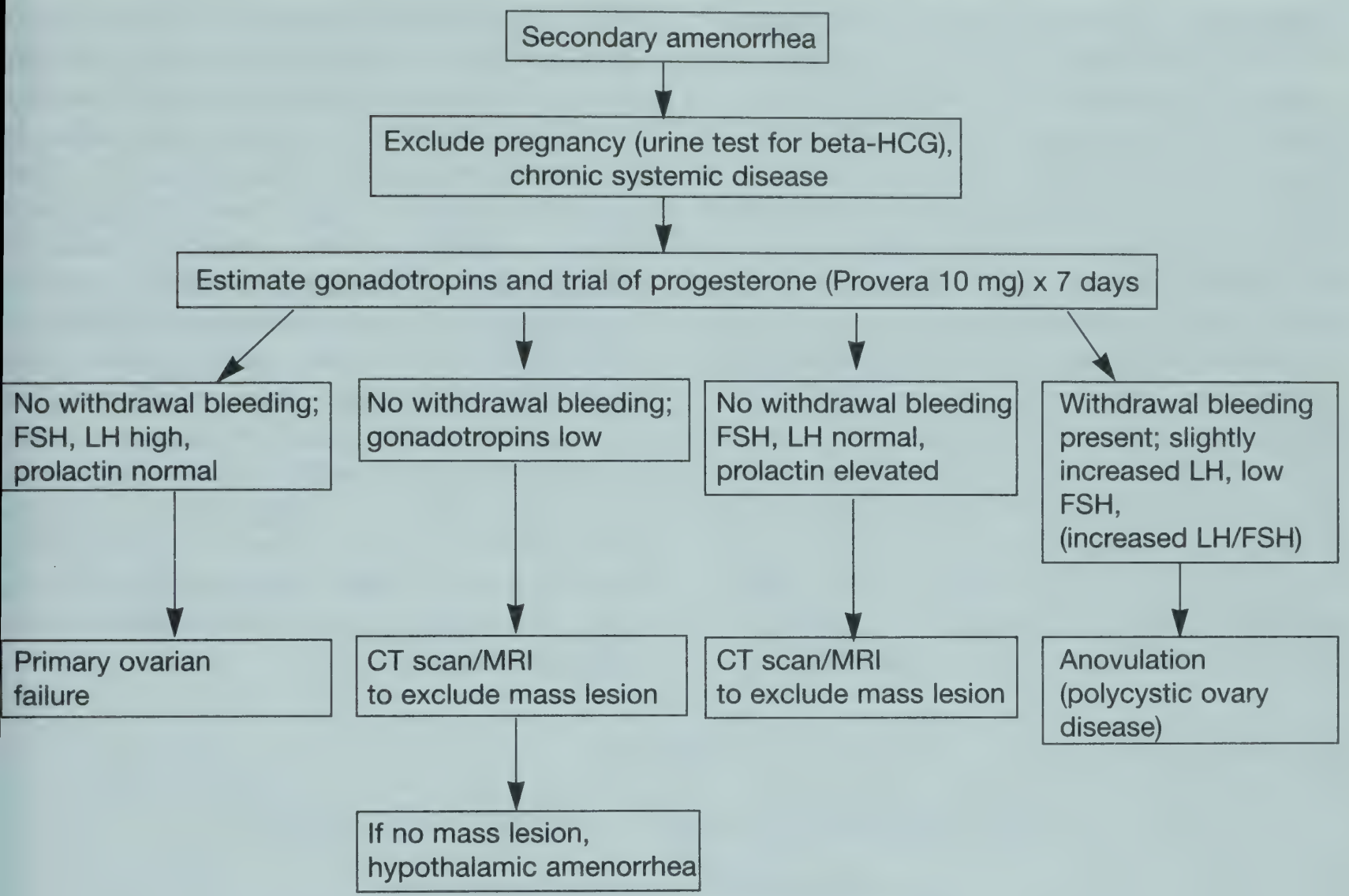


Fig 16.7 Approach to a patient with secondary amenorrhea

ovary disease is the likely etiology and further work-up should include estimation of plasma gonadotropins and pelvic ultrasonography. If there is no withdrawal bleeding and serum prolactin levels are elevated, a CT or MRI scan of the sellar region should be obtained to exlude a *sellar tumour.* If there is no bleeding and the serum prolactin level is normal, the serum levels of gonadotropins help to differentiate a primary ovarian (high FSH, LH) from a primary hypothalamic-pituitary area (low FSH, LH).

Management Treatment of amenorrhea is directed at the specific etiology. Outlet abnormalities of the uterus require surgical treatment. Estrogen replacement is required for primary ovarian failure, gonadal dysgenesis and premature menopause. For women with an intact uterus, a sequential estrogen-progestin combination is preferable; for hysterectomised women, estrogen alone suffices. Oral contraceptives are effective in treating the chronic anovulation of polycystic ovarian disease. Pituitary adenomas are treated with surgical excision, whereas bromocryptine may be effective for prolactinomas.

Approach to a Patient with Impotence

Impotence is the inability to achieve or maintain a penile erection for sexual intercourse. Whereas transient episodes of impotence are not uncommon (such as related to the stress of a honeymoon), this discussion focuses on *persistent* impotence.

Approach Potency depends on the integrity of the neurological, vascular and endocrine systems. It is meaningful to briefly outline the physiology of erection as it illustrates the various steps where malfunction may occur. The flaccid penis is under tonic sympathetic inhibition with vasoconstriction of the smooth muscle of cavernosal arteries and sinusoids. *Erection* begins with central psychogenic and local genital stimuli. Stimulation of efferent parasympathetic nerve fibres from the sacral spinal cord (S2–S4) results in relaxation of afferent penile arteries and constriction of efferent arteries; this results in vascular engorgement of the penis. Tonic contraction of bulbocavernosus, ischiocavernosus and transverse perineal muscles helps to maintain erection. *Ejaculation* is mediated by sympathetic outflow from the spinal cord.

An important component of the sexua impulse is libido. *Libido* is the physiological an mental drive for sexual intercourse. Complet loss of libido can result in impotence, althoug the converse is not true. Loss of libid may be related to drugs (alcohol, tranquilliser opiates, antihypertensive agents) or endocrin disease (hypopituitarism, pituitary tumour hypogonadism). A drug history must always b meticulously obtained in patients wit impotence. Neurologic diseases affecting th sacral spinal cord or vascular disease affectin the aortoiliac, hypogastric or pudendal arteri too can result in impotence. Multipl mechanisms may be operative in mediatin impotence in a condition like diabetes mellitu wherein both vascular and neural pathways ma be involved (Fig 16.8).

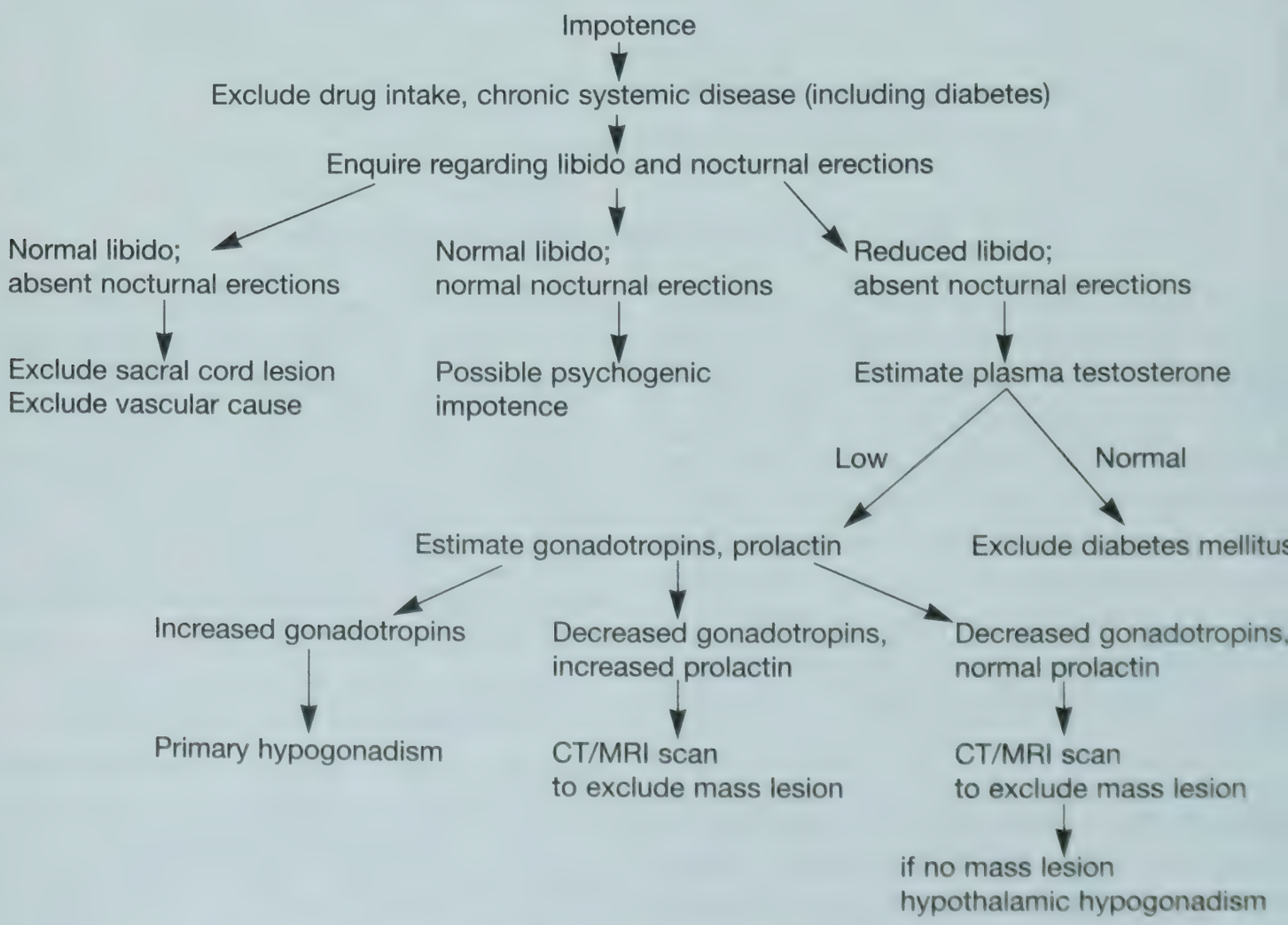


Fig 16.8 Clinical approach and laboratory investigations in an impotent patient

One of the important clues to the etiology of impotence is an enquiry regarding the presence of *nocturnal erections*. If nocturnal erections are present in a patient with impotence, psychological factors (stress) are the likely etiology. Physical examination should include a careful search for signs of hypogonadism (loss of axillary, pubic hair), pea-sized testis (<4 cm, as in Klinefelter syndrome), signs of systemic disease (diabetes, hypothyroidism). A detailed neurlogic examination is also important to evaluate the integrity of sacral spinal cord neural pathways. Peripheral pulses should be palpated for evidence of peripheral vascular disease.

Treatment Treatment depends on the underlying etiology. Endocrine impotence related to hypogonadism responds to testosterone replacement (testosterone enanthate 200 mg i.m. every 2–4 weeks). If a pituitary tumour is the underlying cause, surgical excision is the treatment of choice. Non-endocrine impotence is best managed by referring to a specialist. Vacuum-constriction devices and sex-therapy have been used with variable success.

KEY CONCEPTS

Growth retardation

- ➢ Growth retardation is empirically defined as a height 3 S.D. below the mean for a particular age.
- ➢ Key elements in the history include an enquiry regarding the height of the parents (important for identifying familial short stature), the age at puberty, nutritional status and presence of chronic systemic disease.
- ➢ An assessment of body proportions, bone age and signs and tests of hormonal deficiency permit a distinction between a constitutional delay in growth, hypothyroidism and hypopituitarism.

Hirsutism

- ➢ Hair on the face, upper pubis and chest is dependent on the testicular androgen.
- ➢ Causes of hirsutism include idiopathic, adrenal neoplasia, chronic anovulation, congenital adrenal hyperplasia, and drugs (phenytoin, minoxidil, diazoxide).
- ➢ A careful history is necessary to exclude drug intake. Physical examination must include ascertaining the presence of *defeminisation* (amenorrhea, decreased breast size, loss of female contour) or *virilisation* (frontal balding, clitoromegaly, acne, coarse voice); the presence of either suggests androgen excess.
- ➢ A rapid onset of hair growth and elevated levels of androgens (plasma testosterone levels >3 ng/ml or DHEA >8000 ng/ml) suggest an adrenal neoplasm. Presence of obesity, chronic anovulation, enlarged ovaries and elevated LH levels suggest a diagnosis of polycystic ovary disease. Partial congenital adrenal hyperplasia may also present in a similar manner, and is suggested by elevated 17-OH progesterone levels.
- ➢ Treatment includes cosmetic measures (depilatory techniques) and anti-androgens (spironolactone, cyproterone acetate).

Gynecomastia

- ➢ Causes of gynecomastia include physiologic events (puberty), drug intake (spironolactone, digitalis, cimetidine), Klinefelter syndrome, liver disease or estrogen producing tumours.
- ➢ An assessment of testicular size and karyotype helps identify patients with Klinefelter syndrome. Liver function tests help detect liver disease. Plasma levels of estrogen, LH and testosterone help differentiate between potential causes. If LH levels are elevated but testosterone is low, testicular failure is the likely cause. If both LH and testosterone are low, the etiology is likely to be estrogen production (e.g., tumour, liver disease). If both LH and testosterone are elevated, a neoplastic source (gonadotropin secreting tumour) is likely.

Amenorrhea

- ➢ Amenorrhea may be *primary* (failure of menarche by age 16 years) or *secondary* (absence of menstrual periods for >6 months).
- ➢ As a first step, pregnancy must be excluded. Amenorrhea in a non-pregnant woman may be due to

anatomic defects (of the uterus, vagina or cervix), ovarian failure (gonadal dysgenesis, resistance to FSH; elevated plasma FSH levels >40 IU/L) or the result of chronic anovulation (polycystic ovary disease; hypogonadotropic hypogonadism).

➢ The assessment of plasma estrogen levels and the response to a progesterone preparation may help identify the etiology (withdrawal bleed).

When estrogen production is adequate but there is no withdrawal bleeding (on progesterone administration), an anatomic defect is likely. A physical examination and a pelvic ultrasound may help identify the exact nature.

When estrogen production is adequate and there is withdrawal bleeding, polycystic ovary disease or an adrenal tumour are likely etiologies.

When estrogen production is deficient and there is no withdrawal bleeding, hypogonadotropic hypogonadism may be present. In such patients it is important to exclude a pituitary tumour (CT/MRI of sella).

16.3 Diagnostic methods in endocrinology

Assessment of Endocrine Function

Endocrine status is commonly assessed using *static tests,* which measure levels of hormones in plasma or urine, *dynamic tests,* which assess hormone reserve (stimulation tests) and regulation (suppression tests), and tests which evaluate tissue effects. These tests are often combined judiciously based on the clinical picture and occasionally supplemented with additional imaging studies which permit visualisation of the endocrine organ itself.

Measurement of plasma levels of hormones

Blood levels of hormones are routinely used for evaluating endocrine status. The hormone assay methods vary among laboratories. They generally use highly specific and sensitive antibodies, which facilitates the quantitation of picomolar (peptide hormones) to nanomolar (steroid hormones) plasma concentrations. These tests are generally based on the principle of *competitive inhibition* of a labelled 'known' amount of the hormone by the amount of hormone in a given assay specimen (unknown) for binding to a fixed amount of specific antibody. When a radioactive isotope is used for labelling purposes, the assay is called a *radioimmunoassay* (RIA). Although RIAs are very precise, they are expensive, use radioactivity and are not freely available. An alternative technique, which is easy to perform and which combines precision of measurement with economy, is the *enzyme-linked immunosorbent assay* (ELISA). In ELISA, two antibodies are used which are directed against different epitopes on the hormone. One antibody (*capture antibody*) is usually in a solid phase where it immobilises any hormone. This immobilised hormone is then quantified using the second antibody (*detection antibody*) which is linked to a coloured substance or enzyme that brings about a *colourimetric reaction.*[1]

Certain principles need to be remembered while interpreting blood hormone levels. In order to estimate hormones secreted in a pulsatile fashion into blood (such as LH, FSH), multiple samples should be drawn 20–30 minutes apart. When the hormone being assessed has a circadian rhythm, the level should be interpreted based on that expected at the particular time when the blood sample was obtained. Thus, morning plasma cortisol levels may be twice that of evening plasma levels. Another caveat is that steroids and thyroid hormone are transported bound to carrier proteins. Most conventional assays measure total hormone (free + carrier-bound) in the blood by extracting carrier-bound hormone using organic solvents. Unfortunately, the free hormone (the physiologically active component) is a small proportion of the hormone and changes in carrier protein levels can change 'total' hormone levels without necessarily indicating any change in the 'free' hormone. Hence knowledge of factors affecting carrier protein levels should be considered when

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1 If the signal antibody is linked to a fluorescent compound, a fluorescence microscope can detect the reaction *(immunofluorometric assay).*

'total' hormone levels are interpreted. For example, pregnancy increases levels of thyroxine-binding globulin resulting in increased estimated thyroxine levels, without indicating hyperthyroidism.

Blood levels of most hormones demonstrate a Gaussian distribution. Hence, unless prior levels are known in a patient (which is unlikely), an estimated level may be half of its 'prior' level and still fall within the reference limits. Therefore, blood hormone levels are often interpreted in the light of simultaneously assessed levels of its *effector pair* (thyroxine levels are interpreted along with knowledge of TSH levels). The other 'pair' may be abnormal even if the levels of one are in the 'low-normal' range.

Measurement of urinary excretion of hormones

Sometimes it is advantageous to measure urinary excretion of hormones. For instance, 24-hour urine 'free' cortisol is an excellent measure of 'free' cortisol in the blood.[1] Urine levels of hormones must be interpreted in the context of 24-hour urine creatinine levels (which assesses the adequacy of urine collection) and renal function tests (which measure if renal excretion is altered). Furthermore, urine levels may sometimes not be helpful if the excreted metabolite is from more than one source. One such example is urine 17-ketosteroids; since in men these compounds arise from adrenal and gonadal androgens, an increased urinary level does not help determine the source of a hyperandrogenic state. Lastly, urinary estimation is not useful for hormones excreted into the bile (e.g., thyroid hormones).

[1] Cortisol binding globulin is often saturated in the morning; free (unbound) cortisol gets filtered at the glomerulus and appears in the urine.

Dynamic tests of hormone reserves and regulation (stimulation and suppression tests)

In stimulation tests, a hormone is administere and the response of the target gland is assesse (for example, response of plasma cortisol t ACTH). Alternatively, a drug may b administered which blocks the production o action of an endogenous hormone and th response of its pair (usually a pituitary trophi hormone) is assessed. An example is th *metyrapone test*; the drug inhibits cortiso production and as a response the pituitar increases production of ACTH.

Suppression tests are used to check if hyperfunctioning gland is functioning auto nomously, or whether it responds to feedbac inhibition. The agent administered i suppression tests is usually one which mediate the negative feedback regulation of th concerned hyperfunctioning gland. The degre of inhibition of hormone secretion in response t the administered agent is assessed. An exampl is the *dexamethasone suppression test* (se Chapter 16.7).

Tissue effects

These tests measure the actual tissue response to the hormone. For instance, antidiuret hormone effects can be assessed by estimatin serum and urine osmolalities at rest, and as response to water deprivation.

Imaging tests

Imaging of endocrine glands is importan especially prior to surgical resection, in order t assess which lobe of a gland is hyperfunctionin (parathyroid adenoma versus hyperplasia), an for detecting ectopic hormone production site (ectopic thyroid or chromaffin tissues). Radi isotope scans, CT scans and MRI scans are use for this purpose.

16.4 Neuroendocrine physiology and disorders of the pituitary gland

Growth hormone (GH)

GH is secreted by *somatotrophs* of the anterior pituitary. It is a single polypeptide chain with a molecular weight of 22,000 which is cleaved from a larger precursor molecule. Alternative cleaving of the precursor molecule results in the formation of a variant with reduced immunological and biological activity. A large oligomeric form of the hormone also occurs. The major circulating form of the hormone is the monomeric 22 kD peptide.

GH is stored in secretory granules in a polymeric form. It is released in a pulsatile fashion especially following meals, exercise and during slow wave sleep. Its half-life in plasma is about 30 minutes. Its secretory rate is highest during periods of rapid growth. Levels in plasma tend to decline after the third decade.

GH is necessary for linear growth. Its actions are mediated by a group of hormones called *somatomedins*. Somatomedins are produced in a wide variety of tissues the most important of which is the liver. These hormones are protein-bound and hence have a half-life of upto 18 hours in contrast to the short half-life of GH. In addition to its effect on postnatal growth, GH has important metabolic effects. It acts as an insulin antagonist and causes insulin resistance. It is one of the counter-regulatory hormones which protects against the development of hypoglycemia. GH also increases free fatty acid release from fatty tissue. It promotes the uptake of amino acids for protein building.

GH is primarily controlled by the *hypothalamic GH releasing hormone* (GHRH) which is stimulatory, and *somatostatin* which inhibits its secretion. Various other stimuli act through these primary control mechanisms to alter GH secretion. Hypothalamic dopamine, alpha adrenergic stimulators (including clonidine), hypoglycemia, arginine and exercise stimulate GH secretion through GHRH. Acetylcholine increases GH secretion by inhibiting somatostatin. Acute administration of glucocorticoids stimulates GH release. Chronic administration of glucocorticoids suppresses GH release and accounts for the growth retardation in children on long term glucocorticoids.

Prolactin

Prolactin is secreted by the *lactotrophs* of the anterior pituitary. The predominant form in the plasma is that of a single polypeptide containing 198 amino acids. Higher molecular weight forms of the hormone exist in small quantities in the circulation but do not possess biologic activity.

Prolactin is essential for lactation. It acts on the breasts which have been primed by estrogen and progesterone, to stimulate milk production. During pregnancy, placental estrogens stimulate the growth and secretion of pituitary lactotrophs in preparation for lactation. The high estrogen levels during pregnancy, however, have an inhibitory effect on milk secretion by the breast. Hence, lactation commences after delivery when estrogen levels decline.

Prolactin secretion is primarily under the inhibitory control of dopamine secreted by the *arcuate nucleus* of the hypothalamus. Prolactin secretion is stimulated by thyrotropin releasing hormone (TRH) and vasoactive intestinal polypeptide (VIP). While the physiologic role of TRH-mediated stimulation of prolactin is unknown, it is thought that VIP may be the mediator for suckling induced secretion of prolactin. Sleep and physical/emotional stress also stimulate prolactin secretion.

Thyrotropin (TSH)

TSH is a glycoprotein composed of alpha and beta subunits, produced by the *thyrotrophs* of the anterior pituitary. Its *alpha subunit* is identical to those of LH, FSH and HCG. The *beta subunit* is unique and is detected by TSH immunoassays.

TSH has a trophic effect on the thyroid gland and controls the synthesis and secretion of the thyroid hormones. It acts on a cell surface receptor to increase intracellular cyclic AMP, which in turn initiates the intracellular actions of TSH.

TSH is under dual control. It is stimulated by the hypothalamic *thyrotropin releasing hormone* (TRH) and inhibited by the thyroid hormones.

Currently, TSH levels are measured by an ultrasensitive radioimmunoassay technique which can detect very minute quantities of the hormone; this has now made differentiation between normal and low levels possible. TSH levels can be interpreted only in conjunction with thyroid hormone concentrations.

Gonadotropins

The gonadotropins, that is, follicle stimulating hormone (FSH) and luteinising hormone (LH), are synthesised by the *gonadotrophs* of the anterior pituitary. They are glycoprotein hormones with identical alpha subunits and distinctive beta subunits which are detected by radioimmunoassay.

FSH stimulates the growth and maturation o *granulosa cells* of the ovarian follicle and als increases the activity of *aromatase* whic stimulates estradiol synthesis in these cells. I males, FSH stimulates spermatogenesis.

LH stimulates the *theca cells* of the ovaria follicle to produce androgens, which ar converted to estrogens by the adjacen granulosa cells. LH secretion surges a da prior to ovulation and triggers ovulatio Following this, it contributes to the formation o the corpus luteum. LH stimulates the productio of testosterone by the *cells of Leydig* in th testes.

Hypothalamic *luteinising hormone releasi hormone* (LHRH) stimulates the release of bot FSH and LH by the pituitary. The *pulsati* secretion of LHRH causes pulsatile secretion FSH and LH, whereas the *continuous* secretio of LHRH inhibits the release of both hormone Low doses of estrogen inhibit LHRH and hig doses stimulate its secretion.

Adrenocorticotropin (ACTH)

ACTH is secreted by the *corticotrophs.* It synthesised as part of a large precursor molecu the *pro-opiomelanocortin* which contains, addition to the ACTH molecule, beta lipotrop and melanocyte stimulating hormone. Henc excess ACTH results in excessive cutaneo pigmentation.

ACTH is responsible for the synthesis a release of adrenal corticosteroids. While stimulates aldosterone release by the zo glomerulosa acutely, it is not essential f aldosterone secretion; aldosterone secretion normally controlled by the renin-angioten system.

ACTH is inhibited by the adren corticosteroids and is stimulated by t hypothalamic *corticotropin releasing fact* ACTH is also stimulated by stress, includi surgery, hypoglycemia and psychiat distress.

DISORDERS OF THE PITUITARY GLAND

The pituitary gland is seated in the *sella turcica* of the sphenoid bone. It is composed of an anterior lobe (*adenohypophysis*) and a posterior lobe (*neurohypophysis*). The anterior lobe develops from the proliferation of the cells of the *Rathke's pouch*, an extension of the embryonic oral cavity. The posterior lobe is formed from a diverticulum arising from the floor of the fourth ventricle. The gland is separated from the brain by a thin fold of dura, the *diaphragma sellae*. On either side of the gland are the cavernous sinuses containing the internal carotid artery and the cranial nerves III, IV, V, and VI. The optic chiasma lies superior and anteriorly. The sphenoid sinus is located inferiorly.

The main blood supply to the anterior lobe is from the veins of *hypothalamic-hypophyseal portal circulation,* which are formed by the coalition of the capillaries from the hypothalamus. These veins serve to carry nutrients and hypothalamic releasing hormones which control anterior pituitary secretion. The hormones secreted by the pituitary gland are listed in Table 16.6.

Table 16.6 Pituitary hormones

Anterior pituitary
Prolactin
Growth hormone (GH)
Follicle stimulating hormone (FSH)
Luteinising hormone (LH)
Thyroid stimulating hormone (TSH)
Adrenocorticotropic hormone (ACTH)
Posterior pituitary
Antidiuretic hormone (ADH)
Oxytocin

Disorders of the Anterior Pituitary

Hypopituitarism

Etiology The causes of hypopituitarism are listed below.

1. Pituitary or parapituitary neoplasms
2. Trauma
3. Autoimmune hypophysitis
4. Vascular — postpartum infarction (Sheehan syndrome), apoplexy, carotid artery aneurysms
5. Infiltration — sarcoidosis, histiocytosis, hemochromatosis
6. Infections — meningitis, encephalitis, syphilis
7. Radiation

Diagnosis The clinical diagnosis of hypopituitarism is often difficult due to its insidious onset, slow progression and subtle presentation. Deficiencies of various anterior pituitary hormones occur in predictable succession. GH is the first to be lost and its deficiency manifests in children as growth retardation. LH and FSH are lost next resulting in a decline in gonadal function. This is followed by the loss of ACTH and eventually of TSH. Suprasellar involvement may produce diabetes insipidus due to loss of ADH secretion.

Clinical features (Table 16.7) These include features of endocrine *hormone deficiency,* and in neoplastic disorders, those of *compression or infiltration of the surrounding neural structures* (see section 'Tumours of the pituitary').

Investigations

A. Endocrine assessment: 1) GH and ACTH secretion: *insulin stress test*

Insulin-induced hypoglycemia stimulates pituitary secretion of GH and ACTH. 0.1 u/kg body weight of insulin is administered intravenously and blood samples are drawn at 0, 30, 60, 90 and 120 minutes for measurement of plasma glucose, GH and cortisol (as a measure of ACTH secretion). The plasma glucose should

Table 16.7 Clinical features of hypopituitarism

Hormone deficiency	*Manifestations*
Growth hormone	growth retardation in children fine wrinkling of skin malaise truncal obesity and poor muscle bulk
Luteinising hormone and follicle stimulating hormone	decreased libido infertility amenorrhea in women small soft testes and loss of axillary and pubic hair in men
Adrenocorticotropin	fatigue loss of appetite and weight hypotension skin pallor and depigmentation of areolae loss of axillary and pubic hair in women coma
Thyroid stimulating hormone	cold intolerance weight gain fatigue bradycardia mental sluggishness delayed relaxation of tendon reflexes coma

fall to 40 mg/dl for adequate stimulation of the pituitary gland. A GH level > 10 μg/L and a cortisol level >19 μg/L excludes hypopituitarism. This test is contraindicated in patients with convulsive disorders and heart disease. If there is a strong suspicion of hypopituitarism the dose of insulin should be reduced to 0.05 u/kg.

2) Gonadotropin secretion: *LHRH stimulation test*

A regular menstrual cycle in women indicates normal gonadotropin secretion. Similarly a normal serum testosterone level and sperm count in a male establishes normal gonadotropin production. The LHRH stimulation test is done if the above are abnormal. LHRH 100 μg is given i.v. and blood samples for LH and FSH are drawn at 0, 20 and 60 minutes. Normally, the LH rises to above 10 u/L and the FSH to above 5 u/L.

3) TSH secretion

The serum free T_4 or the *free thyroxine index* are first measured. If these are normal TSH secretion can be assumed to be normal. If free T_4 is low, the TSH is measured: if this is low, then pituitary hyposecretion of TSH exists.

B. Determining the etiology of pituitary hypofunction: The most common cause being pituitary tumours, the following investigations are performed in addition to endocrine assessment:

1. *Visual field assessment* using formal perimetry compression of the optic chiasma/ tracts can be identified by perimetry. Early defects are generally unilateral quadrantic defects in the temporal field; with tumour growth these defects progress to a bitemporal hemianopia. Red colour perception is lost before impaired perception of other colours sets in.

Table 16.8 Treatment of hypopituitarism

Deficient hormone	*Replacement therapy*	*Response assessment*
GH (in childhood)	GH 0.02–0.2 units/kg i.m. thrice a week	Growth assessed by growth chart
ACTH	Prednisolone 7.5 mg at 8.00 am and 2.5 mg at 6.00 pm, oral	Cortisol levels at one hour post morning dose, pre-evening dose and one hour post-evening dose
TSH	Thyroxine 0.1–0.2 mg/day, oral	Serum T_3 level
FSH & LH	*Women*: combined oral contraceptive pill. Gonadotropin replacements are necessary only if pregnancy is desired.	Improvement in libido and secondary sexual characteristics
	Men: Testosterone enanthate 250 mg slow i.m. every 2–4 weeks	Improvement in libido and potency

Skull X-ray: Both PA and lateral views are ecommended. *Erosion* and *ballooning* of the oor of the sella, and *enlargement* of the sella are eatures of macroadenomas of the pituitary. imilar sellar enlargement is also a feature of the *mpty sella syndrome.* Suprasellar calcification a feature of craniopharyngiomas.

CT scan with contrast enhancement is useful identifying pituitary tumours including icroadenomas, and in detecting the empty sella yndrome.

MRI is superior to CT scanning in delineating natomy and detecting suprasellar extension of ituitary tumours.

reatment Treatment involves replacement f the deficient hormones (Table 16.8) and easures to control the underlying cause of ituitary dysfunction. Cortisol replacement hould precede thyroid replacement; thyroid eplacement is likely to precipitate acute adrenal sufficiency in the presence of diminished ituitary reserve by increasing the degradation f cortisol. Cortisol insufficiency masks diabetes sipidus by reducing free water clearance from he body; this may manifest with cortisol eplacement therapy and requires specific eatment (see 'Disorders of the posterior ituitary').

umours of the pituitary

umours of the pituitary are among the ommonest causes of hypopituitarism and account for 10–15 per cent of all intracranial neoplasms. They manifest as pituitary hormonal insufficiency, neurological dysfunction due to compression/invasion of the surrounding structures, and, in the case of secreting tumours, as syndromes of hormonal excess.

Pathology These tumours were originally classified based on *hematoxylin* and *eosin* staining as *acidophilic, basophilic* and the *chromophobes* which do not take up any stain. Prolactin-secreting tumours rich in prolactin granules, and GH-secreting tumours are acidophilic. ACTH-secreting tumours are basophilic. All other tumours including non-secreting tumours are chromophobic. Since this classification provides no definite insight into hormone production it has been abandoned.

Pituitary adenomas are occasionally familial and may occur as part of the Multiple Endocrine Neoplasia I Syndrome. This is an autosomal dominant disorder characterised by the co-occurrence of adenomas of the pituitary and the endocrine pancreas, and hyperplasia of the parathyroid.

Clinical features Pituitary tumours produce endocrine manifestations of hormone excess (in the case of secretory tumours) and features of hypopituitarism from the compression of the surrounding cells. Large tumours also produce compression of surrounding neural structures.

Table 16.9 Clinical characteristics of pituitary tumours

Tumour	*Usual size*	*Clinical features*
Prolactinoma	commonly < 10 mm,	Galactorrhea, amenorrhea, hypogonadism, impotence
	some are > 10 mm	Above + headaches, field defects, hypopituitarism
GH-secreting tumours	medium to large	Change in facial appearance, visual field defects, hypopituitarism, abnormal skull X-rays (90%)
ACTH-secreting tumours	most are small, or show only hyperplasia and not tumour	Central obesity, hypertension, glucose intolerance, cutaneous striae
Post-adrenalectomy ACTH secreting tumour (Nelson syndrome)	large	History of adrenalectomy, hyperpigmentation, sometimes local symptoms
Non-secreting tumours	often large	Headaches, visual field defects, hypopituitarism
Craniopharyngiomas	often very large and cystic	Headaches, visual field defects, growth failure, abnormal calcification in skull X-rays in >50%

Visual field defects are common. Compression of the crossing fibres of the optic chiasma characteristically produces a bitemporal hemianopia. Lateral growth of tumours produces oculomotor palsies. Headaches occur due to stretching of the diaphragma sellae. In rare cases, acute hemorrhage into the tumour occurs (*pituitary apoplexy*) causing severe headaches, nausea and vomiting, oculomotor palsies and meningism. The clinical characteristics are presented in Table 16.9.

DISORDERS OF PROLACTIN SECRETION

The lactotrophs of the anterior pituitary secrete prolactin, a single chain polypeptide hormone.

Hyperprolactinemia

The causes of hyperprolactinemia are listed below. The approach to a patient with hyperprolactinemia is given in Fig 16.9.

Table 16.10 Causes of hyperprolactinemia

Physiologic states
Pregnancy, suckling, sleep, nipple stimulation, stress, coitus

Drugs
Phenothiazines, butyrophenones, thioxanthines, metoclopramide, methyldopa, reserpine, estrogens, opiates, verapamil

Pathologic states
Prolactinomas, adenomas secreting prolactin an other hormones e.g. GH, ACTH,
Disorders causing pituitary stalk compression
Polycystic ovary syndrome
Primary hypothyroidism
Chest wall injury
Renal failure
Liver failure
Seizures

Prolactinomas

Tumours arising from the *lactotrophs* are t most common pituitary adenomas. They a

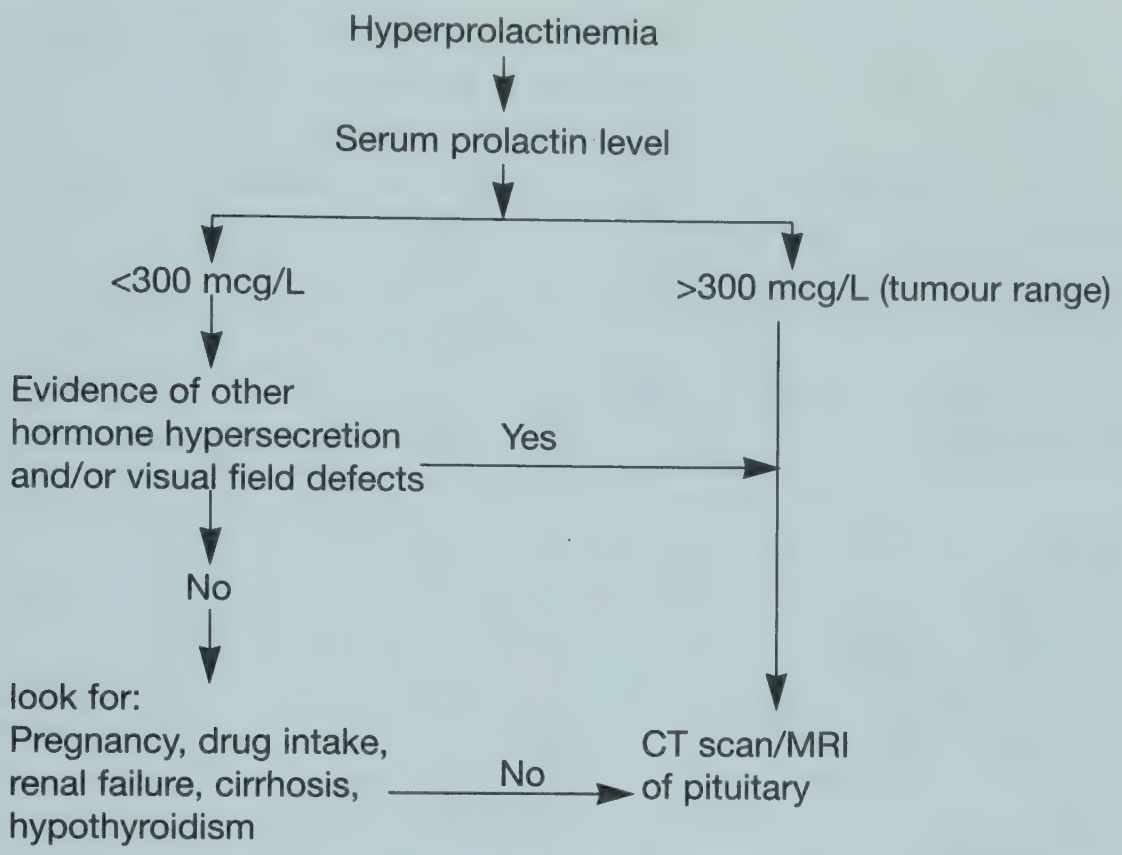


Fig 16.9 Approach to a patient with hyperprolactinemia

classified according to their size as *microadenomas* (<10 mm) and *macroadenomas* (>10 mm). Macroadenomas usually cause significant enlargement of the sella and can be detected on skull X-ray. They also cause headaches, symptoms of pressure effects on surrounding neural structures, and symptoms of deficiency of other pituitary hormones. Microadenomas often cause no significant enlargement of the sella and are detected by CT scan/MRI and exhibit no neurologic or endocrine effects (except hypogonadism caused by inhibition of LHRH secretion). Both types of tumours may or may not be secretory. In the case of secretory tumours the serum prolactin level correlates with their size.

Clinical features Microadenomas are more common than macroadenomas. Women tend to have microadenomas more frequently due to early detection of these tumours from the specific symptoms they produce. They usually present with menstrual irregularities, amenorrhea and galactorrhea. The oral contraceptive pill may precipitate galactorrhea in patients with prolactinomas. Amenorrhea following discontinuation of the oral contraceptive pill is another mode of presentation. A small number of patients present with primary amenorrhea.

Men with prolactinomas usually have sexual dysfunction but often do not seek medical advice and often present with macroadenomas and their resultant neurological complications.

Treatment The presence of microadenomas is not in itself an indication for treatment (Table 16.11). Macroadenomas generally require treatment.

The following treatment modalities are used :

1. Bromocriptine: Bromocriptine is a dopamine antagonist which is effective in hyperprolactinemias of all etiologies. It is useful in the treatment of both micro- and

Table 16.11 Indications for treatment of microprolactinomas

Women	*Men*
Troublesome galactorrhea	Decreased libido
Decreased libido	Impotence
Women desiring pregnancy	Infertility
Women at risk of osteoporosis	

lactinomas. It decreases prolactin levels to normal and shrinks the size of macroprolactinomas. Menses and fertility are restored in most women within two months. The response in men may be delayed. The drug is started at a dose of 1.25 mg at bedtime and the dose is gradually increased to control hyperprolactinemia to a maximum dose of 30 mg/day. Side effects of the drug include nausea and vomiting, nasal stuffiness, postural hypotension and fatigue.

2. Transsphenoidal resection: This procedure is reserved for patients with large tumours with suprasellar extension and persistent visual field defects, and those patients who are unresponsive or intolerant to bromocriptine therapy. Surgery may be combined with radiotherapy in the treatment of macroprolactinomas.

Disorders of Growth Hormone Secretion

Growth hormone is secreted by the somatotrophs of the anterior pituitary. Growth hormone is essential for linear growth. It acts by producing a group of hormones called somatomedins. The prime somatomedin, Somatomedin-C is synthesised in the liver and in bone.

Hypothalamic secretion of growth hormone-releasing hormone (GRH) stimulates GH secretion and somatostatin inhibits it. Other neurotransmitters are also known to influence GH secretion. Dopamine stimulates GH secretion by stimulating GRH.. Serotonin agonists stimulate GH release. Alpha-adrenergic agonists stimulate GH secretion.

Acromegaly and gigantism

Gigantism occurs in individuals exposed to growth hormone excess prior to fusion of the bony epiphyses. Acromegaly occurs in adults. A pituitary adenoma is usually the cause. These tumours often reach the size of macroadenomas by the time the diagnosis is made. In rare cases, GH excess is caused by ectopic secretion of GH by carcinoid tumours and pancreatic islet cell tumours.

Clinical features Growth hormone excess is characterised by the growth of the facial and distal extremity bones and hypertrophy of the skin and subcutaneous tissues in the same regions. The facial appearances of acromegaly are typical and pathognomonic. In addition to cutaneous and osteal changes, other systemic manifestations occur (Table 16.12, Fig 16.10).

Table 16.12 Manifestations of acromegaly

Organ/system	*Features*
Skin	Excessive sweating and greasiness, acanthosis nigricans, hypertrichosis, skin tags
Head and neck	Coarsening of facial features, prominent supraorbital ridges, prognathism, macroglossia, goitre, hollow sounding voice
Cardiovascular system	Hypertension, cardiomyopathy
Skeletal system	Enlarging hands and feet, increased heel pad thickness, osteoarthritis
Muscles	Myopathy
Neurologic system	Carpal tunnel syndrome, visual field defects, hypersomnolence
Genitourinary system	Decreased libido, impotence, infertility, oligomenorrhea, kidney stones
Respiratory system	Obstructive sleep apnea
Metabolic	Hypercalcemia, glucose intolerance, hyperphosphatemia

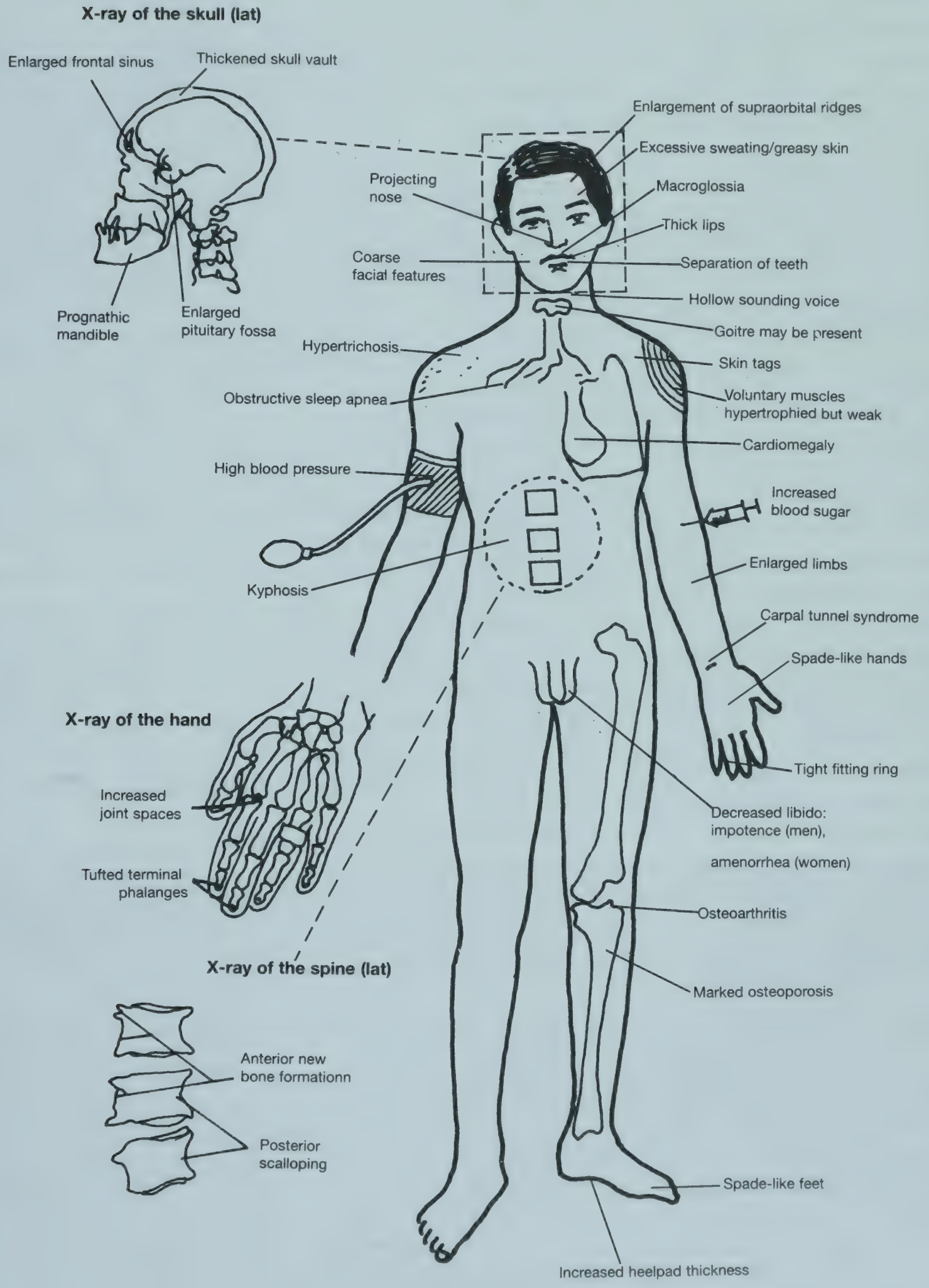


Fig 16.10 Clinical and roentgenographic features of acromegaly

The disease is chronic and slowly progressive. The characteristic physical appearance is due to an increase in the thickness of the skin and subcutaneous tissue as well as due to periosteal bone growth resulting from GH and somatomedin-C excess. Comparing the appearances of the patient to their photographs taken in the past is often helpful in the clinical diagnosis. GH and somatomedin-C increase the secretion from sweat and seborrheic glands. Long-standing exposure can cause organomegaly such as, goitre, hepatomegaly and renal enlargement.

Diagnosis 1. *X-rays of the skull* show an abnormal sella in 90 per cent. In addition, enlargement of the paranasal sinuses, proliferation of the mastoid air cells and prognathism may be seen. Other radiological features include enlargement of the vertebral bodies, and *tufting* of the tips of the terminal phalanges. Soft tissue X-ray of the feet shows a *heel pad thickness* of more than 18 mm in women and more than 20 mm in men.

2. CT/MRI scans of the head are useful in detecting tumour and assessing its size and extent.

3. Growth hormone levels: In healthy subjects exogenous glucose administration normally suppresses GH secretion. A GH level of > 5 µg/L 60 minutes after administration of 100 g of oral glucose is diagnostic of autonomous GH secretion by a tumour.

4) Assessment of anterior pituitary function is essential (refer 'hypopituitarism').

Treatment 1. Transphenoidal surgical removal is the treatment of choice for adenomas secreting GH. GH levels decline rapidly and soft tissue changes disappear soon.

2. Pituitary irradiation with conventional or heavy particle radiation is reserved for patients in whom surgery has failed or is contraindicated, or in those who refuse surgery.

3. Bromocriptine: Dopamine normally stimulates GH secretion. A paradoxical suppression of GH secretion occurs in the case of GH-secreting adenomas. Bromocriptine, a dopamine agonist in doses of 20–60 mg/day is used as an adjunct to surgery or radiotherapy.

4. Octreotide, a somatostatin analogue, is effective in causing tumour regression in 20–50 per cent of patients. The drug is administered at a dose of 50–250 µg every 6–8 hours. Pain and irritation at the injection site, gastrointestinal disturbances, transient steatorrhea and worsening glucose intolerance are known side effects.

The empty sella syndrome

This condition is caused by the herniation of the suprasellar arachnoid space into the pituitary fossa due to partial deficiency of the diaphragma sellae. The pituitary gets compressed and pushed to one side of the sella and a metrizamide-enhanced CT scan shows flow of CSF into the empty sella.

The condition appears to be common in obese, multiparous women who present with headaches. Despite being compressed, the pituitary continues to function normally.

Visual field defects are a rare complication due to the prolapse of the optic chiasma into the empty sella.

The empty sella should be distinguished from the *partially empty sella* following the degeneration of pituitary adenomas. The latter condition is generally accompanied by pituitary hormonal deficiencies, bony erosions of the sella and an increased volume of the pituitary fossa calculated from CT images.

Disorders of the Posterior Pituitary

The posterior pituitary is composed mainly of axons belonging to neuronal cells located in the hypothalamus. The two posterior pituitary hormones, vasopressin (antidiuretic hormone) and oxytocin, are produced as precursor homones in the neuronal cells of the supraoptic and paraventricular nuclei, respectively. They migrate along the axons and are stored in the nerve endings to be released by appropriate stimuli which stimulate the respective neurons (Table 16.13).

Table 16.13 Factors affecting ADH secretion

ncreased ADH	*Decreased ADH*
ncrease in plasma osmolality	Decrease in plasma osmolality
Decrease in extracellular volume	
Pain, stress, exercise	Increase in extracellular volume
Erect posture	
Nausea and vomiting	
Opioids and barbiturates	
Chlorpropamide, carbamazepine, clofibrate	
Angiotensin II	

Oxytocin acts primarily on the breasts nd the uterus. It causes contraction of the yoepithelial cells which line the ductules of the reast and aids in milk ejection from the breast. causes contraction of the smooth muscle of the terus. This action is important in the facilitation f labour.

The chief action of vasopressin or antidiuretic ormone (ADH) is to cause retention of water y the kidneys. It acts on V_2 receptors of the enal collecting tubules, increasing their ermeability to water. As a result, water moves reely from the renal tubules into the hypertonic renal interstitium. This serves to conserve body water and to concentrate urine. ADH also causes vasoconstriction by acting on V_1 receptors located in blood vessel walls.

Disorders of ADH Secretion

Diabetes Insipidus

Loss of ADH secretion or the failure of the kidney to respond to ADH leads to the inability to concentrate urine resulting in *diabetes insipidus* (DI). The etiology of DI is provided in Table 16.14.

Clinical features Polyuria, excessive thirst and polydipsia are the prime features of DI and usually begin abruptly. Polyuria due to the inability to concentrate urine is the primary abnormality. In severe cases the urine output may exceed 20 litres/day. The urine is hypotonic and usually has a specific gravity of less than 1.010.

The loss of water results in a rise in serum osmolarity which in turn stimulates the hypothalamic mechanism for thirst causing patients to drink large quantities of water to match the losses. Cold drinks are often

Table 16.14 Etiology of diabetes insipidus

I. **Central Diabetes Insipidus**
Neoplasms – pituitary tumours, craniopharyngiomas, germinomas, pinealomas, metastases
Infiltration – sarcoidosis, histiocytosis X
Pituitary or hypothalamic surgery
Pituitary irradiation
Head injury
Idiopathic
II. **Nephrogenic Diabetes Insipidus**
Familial nephrogenic DI
Chronic hypokalemia
Hypercalcemia
Drugs – lithium, demeclocycline, methoxyflurane
Chronic renal disorders, obstructive nephropathy, resolving acute tubular necrosis, unilateral renal artery stenosis
Systemic disorders – amyloidosis, multiple myeloma, sickle cell nephropathy, Sjogren syndrome

preferred. If intake of water is restricted due to hypothalamic disease or altered consciousness, serious water depletion and hypernatremia occurs. Electrolyte disturbances do not usually occur in DI as the defect in water absorption is located distal to the final site of electrolyte absorption and exchange, that is, the distal convoluted tubule.

Investigations It is often necessary to establish the definite existence of polyuria in patients complaining of the symptom. A 24-hour urine collection of more than 3 litres confirms polyuria.

1. The simultaneous measurement of urine and plasma osmolality may give a clue to the diagnosis. A low urine osmolality in the presence of a high plasma osmolality is suggestive of DI. A dehydration test should however be performed to make a definitive diagnosis.
2. Assessment of anterior pituitary function (especially to exclude thyroid and adrenal insufficiency) is essential prior to the dehydration test.
3. *Water deprivation test (Fig 16.11):*

The patient is dehydrated from midnight. From 6.00 a.m. the following morning, the patient is weighed every hour and hourly urine samples are collected for measurement of osmolality. In patients with severe DI, that is, urine volumes in excess of 10 litres a day, dehydration is begun in the morning at 6 a.m. to avoid the risk of serious dehydration overnight. The test is terminated if stable osmolalities are obtained (an hourly increase in urine osmolalities <30 mmol/kg for at least three sucessive samples), or if the patient loses more than 2 kg in weight, or if the patient deteriorates clinically.

After the third sample of urine at a stable osmolality is collected, a blood sample for the measurement of plasma osmolality is obtained. A serum osmolality above 288 mmol/kg indicates adequate dehydration. The patient is then given Vasopressin 5 units, or desmopressin 10 mg subcutaneously. A further sample of urine

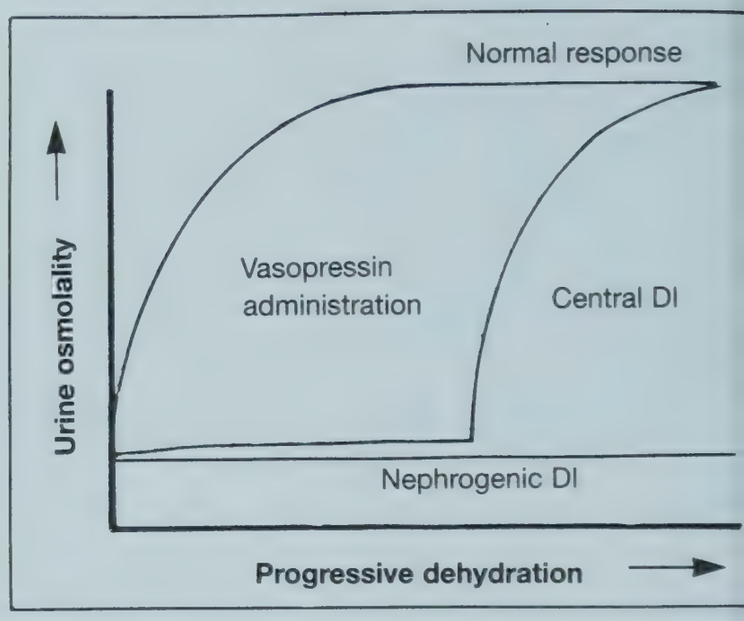


Fig 16.11 Schematic representation of response to wate deprivation test

is collected 30 minutes after the administratio of vasopressin/desmopressin for measurement osmolality.

In normal individuals, the urinary osmolali progressively increases with dehydration an injection of vasopressin causes a rise of less tha 9 per cent in urine osmolality since endogenou ADH is already maximally stimulated. patients with central DI there is usually a increase of more than 9 per cent in urin osmolality following the injection of vasopressi In nephrogenic DI, the urinary osmolality fai to rise following dehydration and after th injection of vasopressin.

Differential diagnosis DI should be differe tiated from other causes of polyuria like diabet mellitus, salt-losing nephropathies and diuret abuse (Fig 16.12).

Compulsive water drinking or *psychogen polydipsia* should be excluded. This disord usually occurs in middle-aged women who oft have an underlying psychological proble requiring antipsychotic drugs. They drink lar quantities of water which reduces plasma osm

lality and supresses ADH secretion, resulting in hypotonic polyuria. The diagnosis is evident from the low serum and urine osmolalities. During the dehydration test these patients may require prolonged water deprivation to achieve a serum osmolality of >288 mmol/kg. They show no rise in urine osmolality in response to exogenously administered vasopressin.

Treatment Treatment of central diabetes insipidus consists of hormonal therapy to replace ADH, or in partial hormone deficiency the use of drugs which increase the quantity of ADH released by the posterior pituitary.

Nephrogenic diabetes insipidus is treated by causing mild dehydration with thiazides (Table 16.15).

Syndrome of Inappropriate ADH secretion (SIADH)

Normally, ADH secretion occurs appropriately in response to salt-retaining states (congestive

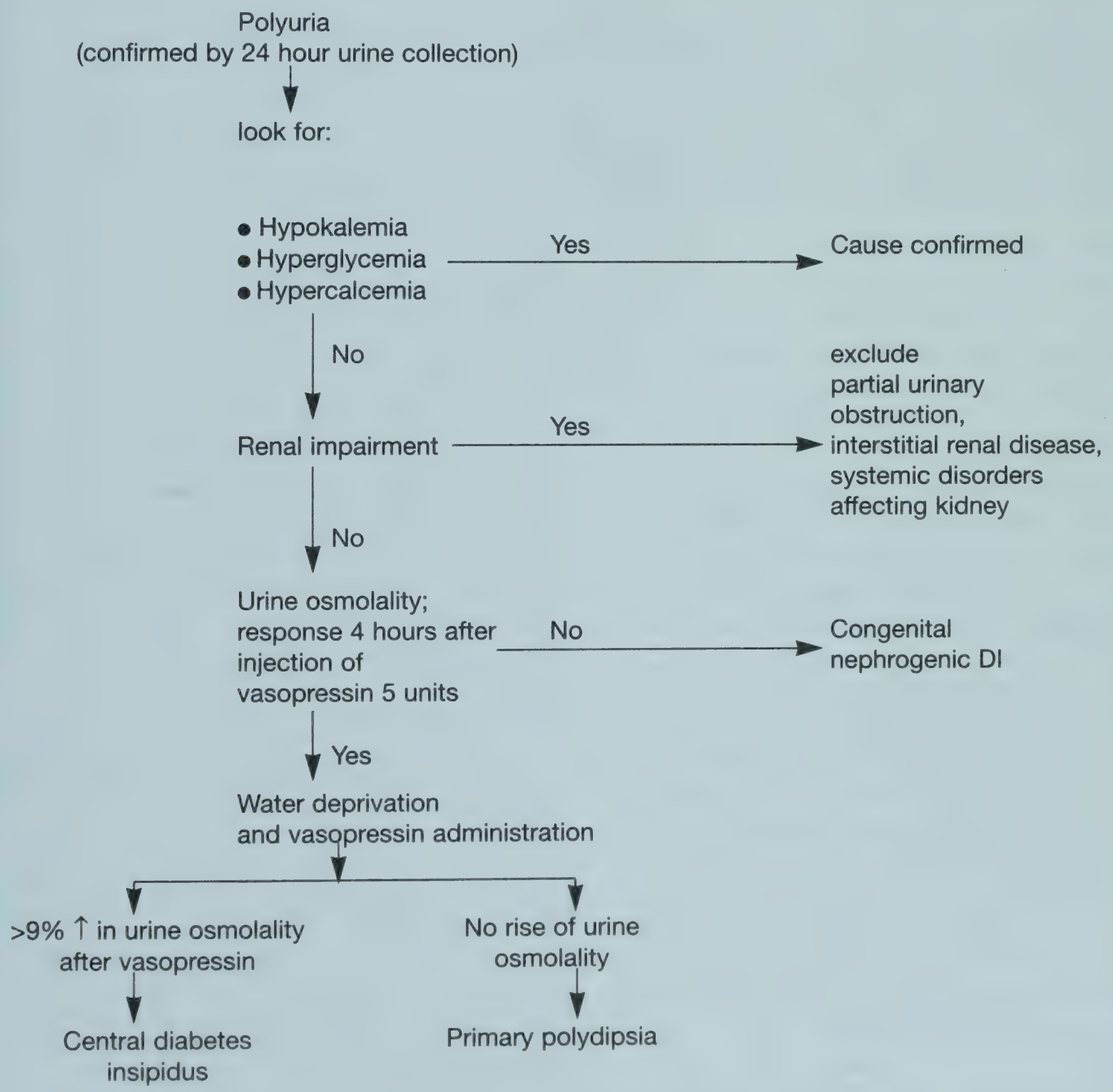


Fig 16.12 Approach to a patient with polyuria

Table 16.15 Treatment for diabetes insipidus

Drug	*Dosage*	*Duration of action*
Central Diabetes Insipidus		
Aqueous vasopressin	5–10 units subcutaneously	3–6 hours
Desmopressin	10–20 µg intransally or 1–4 µg s.c.	12–24 hours
Vasopressin tannate in oil	5 units i.m	24–72 hours
Chlorpropamide	200–500 mg/day	
Clofibrate	500 mg four times a day	
Carbamazepine	400–600 mg/day	
Nephrogenic Diabetes Insipidus		
Hydrochlorothiazide	50–100 mg/day	24 hours
Chlorthalidone	50 mg/day	24 hours

heart failure, cirrhosis, nephrotic syndrome) and in response to volume depletion of any etiology, including adrenal insufficiency. The inappropriate secretion of ADH occurs in the absence of such physiologic stimuli in several clinical states. The causes of SIADH are listed in the box.

The excess ADH secretion may occur from ectopic sites like the lung or neoplastic tissue. Stimulation of the neurohypophysis may account for the ADH excess associated with CNS diseases and some of the drug-induced SIADH.

The excessive release of ADH causes renal reabsorption of water (causing hyponatremia) and concentrates urine despite a low plasma osmolality. The blood volume increases and this in turn suppresses the renin-angiotensin system and stimulates the release of atrial natriuretic peptide resulting in the continued excretion of sodium in the urine. The dilution of plasma causes a drop in the serum electrolytes, urea and creatinine, and uric acid. Despite hypervolemia, blood pressure remains normal.

Clinical features The clinical features of SIADH are due to hypoosmolality resulting

Causes of SIADH

I **Neoplasms**
- Small cell carcinoma of the lung
- Lymphomas
- Others– carcinoma of the pancreas and duodenum, thymoma

II **Pulmonary diseases**
- Pneumonia
- Lung abscess
- Tuberculosis
- Empyema
- Chronic obstructive airways disease

III **Central nervous system diseases**
- Skull fracture
- Subdural hematoma
- Subarachnoid hemorrhage
- Cerebral infarction
- Encephalitis
- Meningitis
- CNS involvement in lupus erythematosus
- Guillain-Barre syndrome

IV **Drugs**
- Chlorpropamide
- Carbamazepine
- Cyclophosphamide
- Clofibrate
- Vincristine and vinblastine
- Narcotic analgesics
- Tricyclic antidepressants
- General anesthesia

V **Miscellaneous**
- Hypothyroidism
- Positive pressure ventilation

m a low plasma sodium. The low osmolality uses shift of water from the extracellular the relatively hyperosmolar intracellular mpartment; this is particularly detrimental to brain. Initial symptoms are non-specific with orexia, nausea and vomiting being prominent. ter, cerebral symptoms of restlessness, itability, confusion, convulsions and coma pervene. The symptoms are prominent if the ness develops rapidly. Edema is conspicuously sent.

agnosis The diagnosis of SIADH is spected in patients with plasma hypo-molality and an inappropriately concentrated ine (>300 mmol/kg). The diagnosis is made ter excluding other causes of hyponatremia.

The following should be excluded before nsidering SIADH:

Diuretic therapy
Edematous states—heart failure, cirrhosis, nephrotic syndrome
Adrenal insufficiency
Hypothyroidism
Renal artery stenosis
Primary polydipsia

ater load test: The definitive diagnosis is made assessing the ability of the patient to excrete water load.

The test is performed only after ascertaining ormal renal function, and after the above entioned conditions have been excluded. The rum sodium should be above 125 mmol prior commencing the test, or should be corrected to this level by dehydration or cautious administration of hypertonic saline.

The patient is given a water-load of 20 ml/kg to drink (upto a maximum of 1500 ml) over a period of 15 minutes. Hourly urine samples are collected and their volume and osmolality measured. Normally, 65 per cent of the water-load is excreted in 4 hours and 80 per cent in 5 hours. The urine osmolality falls to < 100 mmol/kg in the second hour. In patients who do not excrete the water load, no further water intake is allowed for the day to obviate water intoxication.

Plasma ADH levels can be measured. The levels are raised in SIADH despite the water-load. ADH is undetectable in edema states. A thorough search for the underlying cause is necessary as it often determines the prognosis of the condition.

Treatment 1. Fluid restriction to 750–1000 ml/day is essential. This amount is less than the total urine output plus insensible losses, and results in a negative fluid balance. This gradually raises the serum sodium levels.

2. Demethylchlortetracycline (Demeclocycline) is an inhibitor of ADH and is used in doses of 900–1200 mg/day.

3. Hypertonic saline is administered in patients with severe confusion convulsions or coma. 200–300 ml of 5% sodium chloride solution is administered over 4 hours. Rapid administration is known to precipitate central pontine myelinolysis.

4. Identifying and treating the underlying cause is the definitive treatment.

KEY CONCEPTS

Hypopituitarism

- In this condition there is deficiency of one or more hypophyseal hormones. The etiology may be a tumour (adenoma, craniopharyngioma, metastatic), trauma (post-head injury), infiltration (granulomatous disease, e.g. sarcoidosis), inflammation (autoimmune) or infarction (postpartum [Sheehan syndrome]).
- Symptoms vary according to the age of the patient and the deficient pituitary hormone. Thus, GH deficiency results in growth retardation in a child but may be asymptomatic in an adult. TSH deficiency results in hypothyroidism (without goitre). Gonadotropin deficiency manifests as amenorrhea and incomplete development of secondary sexual characteristics in women; in men, reduced potency and libido are the features. ACTH deficiency results in adrenal insufficiency (in contrast to Addison's disease, there is no hyperpigmentation or electrolyte disturbance). Prolactin deficiency presents as failure of lactation in women, and as loss of libido in men.
- Diagnosis is by measurement of serum levels of pituitary hormones and tests of hormones produced by the end-organs (thyroid, adrenal and ovaries). CT or MRI scans help identify pituitary tumours.
- Management consists of treating any underlying cause (e.g., resection of tumour) and hormone replacement.

Hyperprolactinemia

- Defined as a plasma level >20ng/ml, hyperprolactinemia may be *physiologic* (pregnancy, lactation, emotion), or *pathologic* (idiopathic, pituitary microadenoma, hypothalamo-hypophyseal stalk disease).
- In women, hyperprolactinemia results in amenorrhea, galactorrhea and infertility. In men the manifestations are reduced libido and impotence.
- Laboratory investigations (besides plasma levels) include CT/MRI scan to evaluate the sella turcica.
- Management of a prolactinoma depends on the size and presence or absence of symptoms. Small asymptomatic prolactinomas may be followed up. If the tumour is large or if the patient desires pregnancy, several treatment options are available: medical therapy with bromocryptine, radiation and surgery.

Acromegaly

- In this condition there is hypersecretion of GH resulting in the overgrowth of bones and soft tissues. It is usually the result of a benign acidophil macroadenoma.
- Clinical manifestations in an adult include coarse features, prognathia, macroglossia, the enlargement of hands and feet, increased sweating and hypertension. Onset in childhood results in gigantism.
- Radiologic features include enlarged paranasal sinuses, tufting of phalanges, increased heel-pad thickness, and enlargement of the sellar fossa. A high plasma GH level which is not suppressed with a 100 g oral glucose load is diagnostic. CT/MRI are ideal for the evaluation for a sellar tumour.
- Treatment options include surgical hypophysectomy, pituitary irradiation; bromocryptine and octreotide are useful adjuncts to therapy.

Diabetes insipidus

- In DI there is an inability to produce concentrated urine due to complete or partial deficiency of arginine vasopressin (*central DI*; causes include idiopathic, surgery, head trauma, tumour, sarcoidosis) or renal unresponsiveness to AVP (*nephrogenic DI*; causes include obstructive uropathy, drugs [e.g. lithium], familial, hypokalemia).
- Clinical features include polyuria, polydipsia and nocturia. Potential complications include dehydration and confusion.
- As a first step in the investigations diabetes mellitus and chronic renal failure should be excluded and polyuria documented. If the P_{Osm} is >295 mOsm/kg and the U_{Osm} is <295 mOsm/kg, DI is likely. The response of U_{Osm} to a water deprivation test and a subsequent injection of AVP helps in the differential diagnosis.
  - The normal response is an increase in U_{Osm} on dehydration with no further increase with AVP.
  - In central DI, U_{Osm} does not increase on dehydration but increases by >9% with AVP (usually the increase in complete central DI is >50%)
  - In nephrogenic DI, U_{Osm} does not increase on dehydration or with AVP.
- In psychogenic polydipsia, AVP causes an increase <9% in U_{Osm}.
- Management of central DI includes treatment of any underlying cause and administration of DDAVP, or chlorpropamide. Nephrogenic DI is best managed with the use of thiazide diuretics.

SIADH

- SIADH refers to an elevation of plasma AVP levels in the absence of any appropriate osmotic or hemo

dynamic stimuli. The etiology is increased hypothalamic secretion (pulmonary disease: pneumonia, TB; CNS disease: stroke, head injury; drugs: chlorpropamide, carbamazepine, vincristine; hypothyroidism) or ectopic production (small-cell lung cancer).

➢ Patients of SIADH are usually clinically normovolemic and do not have edema.

➢ Elevated AVP results in hyponatremia, hypotonic plasma and a paradoxically concentrated urine. U_{Na} is >20 meq/L. Clinical symptoms are related to the severity of hyponatremia. It is important to exclude CHF, renal failure and hepatic cirrhosis (conditions with appropriate ADH secretion and volume overload).

➢ Treatment consists of water restriction, or demeclocycline (if water restriction is not possible). Hypertonic saline infusion may be occasionally required; avoid rapid correction to obviate the hazard of pontine myelinolysis.

16.5 Diseases of the thyroid gland

The Thyroid Gland

The thyroid gland is the largest endocrine gland in humans and weighs about 20 grams. Embryologically, it originates as a thickened plate of epithelium at the base of the pharynx.

As the gland descends to occupy its usual position in the neck, it may retain its connection to the base of the tongue by the *thyroglossal duct.* Portions of this structure may fill with fluid and give rise to thyroglossal duct *cysts.* There may be regions of *accessory* thyroid tissue anywhere along this duct, and also in the superior mediastinum.

The basic structure of the gland consists of follicles of varying size which are lined by cuboidal epithelial cells called follicular cells. The lumen of these follicles is filled with a proteinaceous material called *colloid,* which is rich in a glycoprotein called *thyroglobulin.* The follicles are the site for thyroid hormone synthesis. Cells which synthesise *calcitonin* are scattered in between the follicles and are called *C cells.* The functions of calcitonin are not fully understood, though its secretion is increased in response to hypercalcemia and it is possible that this has a physiologic role to protect against the development of acute hypercalcemia.

Physiology *Iodine* is the key element in the synthesis of thyroid hormone. The follicular cells in the thyroid gland are able to actively concentrate iodine from the extracellular fluid. They *organify* inorganic iodide (I^-) by the action of the enzyme thyroid peroxidase, to organic iodine (I_2). A number of substances act as competitive inhibitors of *iodine transport* in these cells. They include anions such as perchlorate, thiocyanate, and pertechnetate, and drugs such as propylthiouracil and carbimazole. The most important physiological regulator of iodine transport by the follicular cell is the *thyroid stimulating hormone* (TSH). The follicular cells also synthesise thyroglobulin, which is transported to the lumen. The final biosynthesis of thyroid hormone occurs extracellularly in the lumen of the follicle. Thyroglobulin has the amino acid tyrosine incorporated into its structure. Iodine binds to the tyrosine residues to form monoiodotyrosines (MIT) and diiodotyrosines (DIT). The MIT and DIT combine (*couple*) to form the two biologically active hormones *thyroxine* or T_4 and triiodothyronine or T_3 (Fig 16.13). Though some of the circulating T_3 is released directly from the thyroid, it is estimated that approximately 85 per cent of the circulating T_3 is the result of formation in the periphery by the *deiodination* of circulating T_4. Some of the T_4 is also deiodinated at a different site on the molecule, to an inactive product called *reverse T_3* (rT_3). Antithyroid drugs (propylthiouracil and carbimazole) also act to prevent the coupling reaction. The thyroid hormones are released into circulation after synthesis.

The thyroid gland is under the control of the hypothalamic–pituitary axis. The anterior pituitary synthesises thyrotropin (TSH), which, as the name suggests, stimulates the thyroid

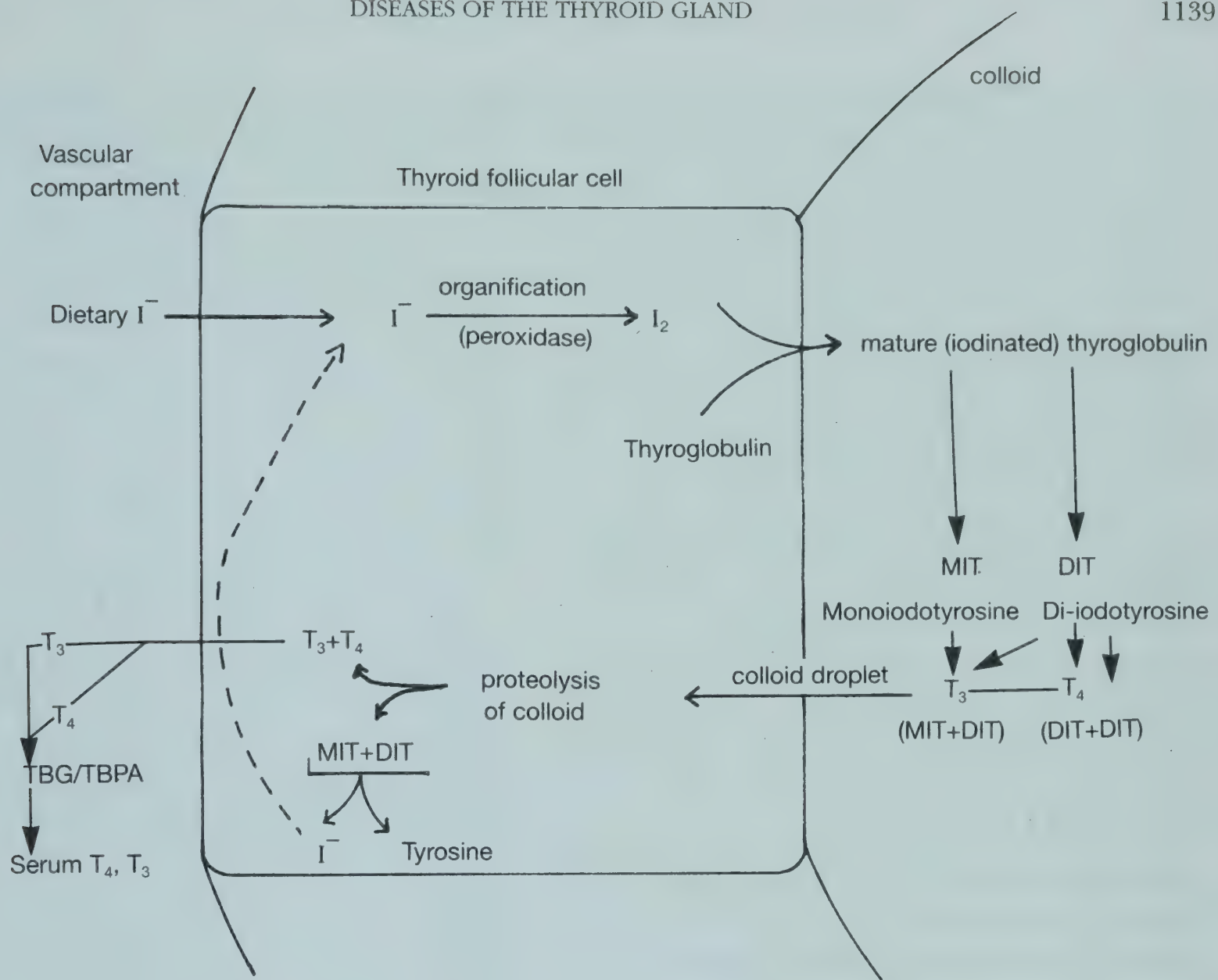


Fig 16.13 Biosynthesis of the thyroid hormones

gland to produce more hormone. TSH secretion in turn is regulated by *thyrotropin releasing hormone* (TRH), a tripeptide, synthesised by the hypothalamus. TSH is a glycoprotein hormone with two peptide chains designated alpha and beta, which are linked by non-covalent bonds. The alpha subunit is common to other glycoprotein hormones (follicular stimulating hormone, leuteinising hormone, and chorionic gonadotropin). Though the presence of the alpha subunit is essential for the activity of these hormones, the beta subunit confers biological specificity. Thyroid hormones exert a powerful negative feedback by inhibiting the production of TSH by the anterior pituitary (Fig 16.14). In hypothyroidism, TSH levels are elevated due to thyroid gland dysfunction (primary hypothyroidism) as serum levels of thyroid hormones are low, and negative feedback is decreased. Besides primary hypothyroidism, serum TSH can be elevated in iodine deficiency, since TSH allows the thyroid follicular cells to take up

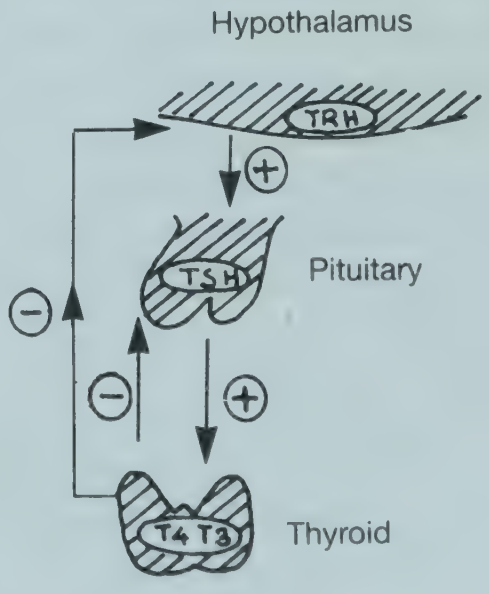


Fig 16.14 Schematic diagram of hypothalamic-pituitary-thyroid function

iodine more efficiently. Other rare causes of elevated TSH levels include a TSH synthesising pituitary adenoma, and thyroid hormone resistance, both of which are associated with a defect in the negative feedback mechanism and elevated levels of circulating thyroid hormones. In the former, this occurs due to loss of differentiation of the adenoma cells, and in the latter because the pituitary and the peripheral tissues are resistant to the biological effects of thyroid hormone (presumably due to a defect in the thyroid hormone receptor). In conditions associated with high circulating levels of thyroid hormones, TSH secretion by the pituitary is suppressed and serum TSH levels are low. TSH synthesis may also be reduced if the pituitary is destroyed by tumour invasion or infarction. Severe illness, starvation and certain drugs (such as corticosteroids and dopamine) inhibit TSH release by the pituitary.

The follicular cells respond to TSH by becoming columnar and increasing the rate of biochemical reactions associated with the synthesis of thyroid hormone. Chronic TSH stimulation leads to hypertrophy and hyperplasia of the follicular cells, and enlargement of both the lobes of the thyroid. The follicles become depleted of colloid and the hyperplastic lining cells may form multiple layers, and sometimes form papillary projections into the follicle. Conversely, under conditions associated with deficiency of TSH secretion, such as pituitary disease and exogenous thyroid hormone treatment, the follicles are distended with colloid, and the lining cells become flattened.

The thyroid hormones are protein-bound while in circulation, but dissociate rapidly prior to entry into the cells, and only the unbound forms bind to the receptor. *Thyroxine binding globulin* (TBG) carries about 70 per cent of the circulating T_4 and T_3, by virtue of its high affinity for the thyroid hormone. *Thyroxine binding prealbumin* (TBPA) binds only about 10 per cent of the hormones, but is responsible for much of the *immediate* delivery of T_4 and T_3 to the cells. This is because its lower affinity for these hormones results in more rapid dissociation. Serum albumin binds about 15–20 per cent of the hormones, but with even lower affinity. Minor fractions are transported by various lipoproteins. Overall, more than 99 per cent of both T_4 and T_3 are bound to plasma proteins. All the major proteins responsible for thyroid hormone transport bind T_4 more avidly than T_3, which means that T_3 tends to dissociate more easily at the cell surface. T_3 also has more biologic activity than T_4 and is, therefore, responsible for most of the metabolic activity.

Thyroid hormones interact with receptors in the cell nucleus, and their main effects are on cellular metabolism and development. They reach the cell nucleus by diffusion through the plasma membrane and also by an active process known as *endocytosis*. The exact mechanisms for the varied effects of the thyroid hormones is not fully understood. It has been shown that the complex of the thyroid hormone with its receptor regulates the expression of various genes. This regulation is achieved by the binding of the receptor-hormone complex to the *thyroid response element* (TRE) of the particular gene. The TRE is a nucleotide sequence that occurs in the 5' region of the T_3 target genes, and the binding of the receptor-hormone complex to this region is necessary for gene transcription to take place. In this manner thyroid hormones regulate the synthesis of various cellular proteins and enzymes. One of the important functions of the thyroid hormones is the stimulation of *cellular respiration*. This may occur through some direct effects on the mitochondria. They also have an important role in *morphogenesis* (structural development) of the brain, liver, lung and heart ventricle. *Myelination* of the central nervous system requires the presence of thyroid hormones. In addition, thyroid hormones also stimulate *somatic growth* in the postnatal period and may act synergistically with growth hormone. For this reason children with hypothyroidism show delayed growth.

Physical examination Palpation of the thyroid gland is often an area neglected in the physical examination of a patient. Thyroid palpation yields substantial information regarding the *size* of the gland and presence of any *nodules,* and is essential to the interpretation of laboratory data and imaging studies. The gland is most easily seen on tilting the patient's head backwards. It moves when the patient swallows, since the gland is attached to the *pretracheal fascia.* The thyroid can be palpated by either standing behind the patient, or with the examinar facing the patient. The neck should be slightly flexed to relax the muscles, and patient may be asked to sip some water after the gland has been located and palpated, to confirm the movement of any abnormalities felt to be in the the thyroid. Normally, the *isthmus* of the gland lies just beneath the cricoid cartilage, and both the lobes rise up on either side of the isthmus. The gland may be felt to be tender and enlarged in subacute thyroiditis. Single nodules may be felt in patients with thyroid adenomas, cysts or thyroid cancer. Patients with cancers may also have associated cervical lymph node enlargement, so this should be carefully looked for. Multiple nodules may be felt in multinodular goitres, though often the thyroid surface is felt to be irregular and no distinct nodules can be palpated. In some patients the thyroid may be 'low-lying' and an enlarged thyroid may be difficult to feel as it may lie *substernally*. Such a gland may cause compression of the trachea, esophagus and the mediastinal vessels (the thoracic inlet). If an enlarged retrosternal thyroid does not cause compression, it may be induced to cause these pressure signs by the patients lifting their arms above their heads, thereby raising the goitre into the thoracic inlet. This is known as *Pemberton's maneuver*, and results in facial plethora, distended neck veins, and sometimes stridor. The thyroid should be auscultated specially if it is enlarged. In patients of Grave's disease, a systolic and diastolic murmur (*bruit*) or a continous low pitched sound (venous hum) may be heard.

Laboratory assessment The development of the principles of radioimmunoassay (RIA) in the early 1970s has provided the basis for the present day laboratory assesement of the levels of many hormones including the thyroid hormones and TSH. The principle of the RIA is simple. The first step is the production of a suitable antibody to the hormone which is to be incubated with the patient serum containing the unknown quantity of hormone. The purified radioactive hormone and the hormone in the test serum compete for the same binding sites on the antibody. The amount of radiolabelled hormone which binds to the antibody is inversely proportional to the concentration of the hormone in the unknown sample. An antibody which is bound to the hormone is separated by a variety of methods. The amount of radioactivity from this antibody hormone complex is measured. The concentration of the hormone in the unknown sample can be calculated by using different concentrations of unlabelled hormone in a similar assay. Many of the older tests for TSH, T_4, and T_3 use a radioimmunoassay using the above principles. With the radioimmunoassay test the detection limit of the TSH is around 1 mU/L, so it is difficult to differentiate a normal TSH from a low TSH as would be seen in thyrotoxicosis. To do this one would require a test with a sensitivity to detect variations in TSH in the magnitude of 0.1 mU/L. With the newer tests, such as the *Immunoradiometric assay* (IRMA), the sensitivity and specificity is increased greatly to these levels, and it is possible to measure TSH levels which are below or above normal. These more sensitive tests use an excess amount of monoclonal antibodies as compared to polyclonal antibodies used in the RIA tests. Often two monoclonal antibodies of different specificities are used, and these bind to different epitopes on the peptide to be analysed.

This greatly increases the sensitivity and specificity of the assay, and is referred to as the *sandwich assay.*

The above tests generally measure total concentrations of T_4 and T_3. As mentioned earlier, only the free hormone, or the hormone not bound to plasma proteins, is the active form. Alterations in hormone-binding proteins would alter total hormone levels, but do not necessarily change levels of the free hormones. Examples of such situations are oral contraceptive pills and pregnancy where the levels of TBG are elevated, thereby giving high values of total thyroid hormones, with normal levels of free hormones. On the other hand, nephrotic syndrome may cause low levels of TBG leading to low total hormone levels, though free hormone levels may be normal.

Free thyroid hormones can be measured in blood, but these tests are expensive and are not generally available. An index of free thyroid hormone levels can be estimated by a test called the *T_3 resin uptake test.* In this test radiolabelled T_3 is added to a sample of the test serum to which a solid matrix or 'resin', (which is capable of binding T_3) has been added. The T_3 in the patient's serum competes with the radiolabelled T_3 for the binding sites on the TBG in the patient's serum. If the level of T_3 in the test sample is very high, or the levels of TBG in the test sample is very low, there will be very few sites empty for the radiolabelled T_3 to bind to the TBG. As a consequence most of the radiolabelled T_3 will bind to the resin. Conversely, if the level of T_3 in the test sample is low or the TBG level is high, most of the radiolabelled T_3 will bind to the TBG in the sample, and there will be little available to bind to the resin (Fig 16.15). The percentage of radiolabelled T_3 added to the sample which is bound to the resin can easily be measured by measuring the radioactivity in the resin. This percentage is called the *T_3 resin uptake.*

Though radioactive T_4 can also be used to calculate such an uptake, T_4 binds much more strongly to TBG than to resin, and hence the assay using labelled T_3 gives more reliable results.

If the values of the T_3 resin uptake and the total T_4 are known, a *free thyroxine index (FTI)* can be calculated. A knowledge of the former two values also tells us about the degree of thyroid hormone binding to the serum proteins in the sample (Table 16.16).

THYROTOXICOSIS

The term *thyrotoxicosis* is used to signify a state characterised by excess of circulating thyroid hormones. This can occur due to a variety of causes, one of which is *hyperthyroidism* where the thyroid shows sustained hyperfunction to produce excess amounts of hormone. Though hyperthyroidism is the most common cause of thyrotoxicosis, there are other important causes and these are detailed below.

Table 16.16 Relationship between T_3 resin uptake and free thyroxine index

Cause	*Total T_4*	*T_3 resin uptake*	*Free thyroxine index*
Increased TBG	increased	decreased	normal
Graves' disease or exogenous thyroid hormone intake	increased	increased	increased
Decreased TBG levels	decreased	increased	normal
Hypothyroidism	decreased	decreased	decreased

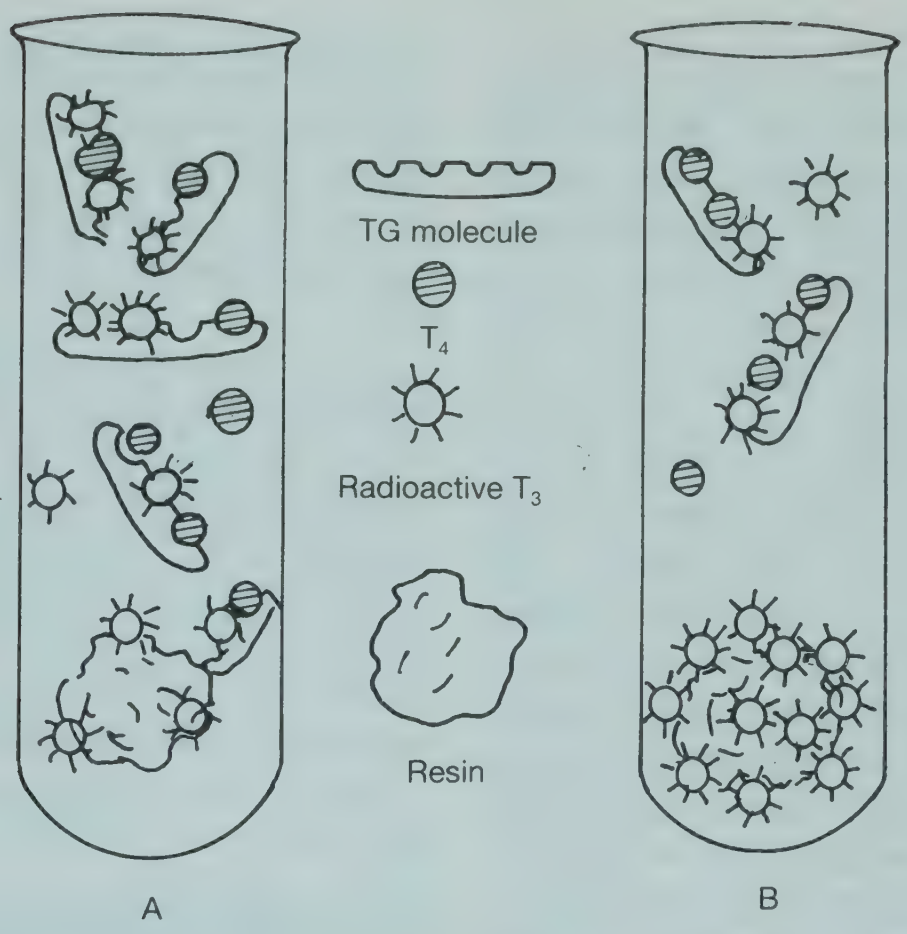


Fig 16.15 Principle of the T_3 resin uptake test
A In situations with excess TBG or low T_4 levels, less radioactive T_3 binds to resin
B TBG deficiency states and/or T_4 Excess leads to more radioactive T_3 to bind to resin

Causes of thyrotoxicosis

1. *Hyperthyroidism*
   - Graves' disease
   - Toxic nodular goitre
   - Solitary toxic adenoma
2. *Excess release of thyroid hormone from inflamed thyroid*
   - Painless or silent thyroiditis
   - Postpartum thyroiditis
   - Subacute (painful) thyroiditis
3. *Extrathyroidal source of hormone*
   - Exogenous thyroid hormone use
   - Ectopic thyroid tissue, as in dermoid tumours of the ovary

Among the causes of spontaneously-occurring thyrotoxicosis, Graves' disease is the most common cause in the developed countries, with most other cases being caused by a toxic nodular goitre. In India, toxic nodular goitre is the most common cause of thyrotoxicosis.

The clinical manifestations of thyrotoxicosis are probably a result of the effect of thyroid hormone on increased cellular metabolism, and the direct effect of thyroid hormone on various organ systems. Thyroid hormones appear to increase the sensitivity of many organs to catecholamines which are secreted by the sympathetic nervous system and the adrenal gland. Moreover the many of the effects of thyroid hormone are synergistic to the effects of catecholamines, and so thyroid hormone excess leads to a state similar to that seen with sympathetic overactivity. This manifests as symptoms of anxiety, tremor and palpitations. The associated eye sign of *lid lag* is due to the inability of the levator palpebrae superioris to relax. This is one of the upper eyelid muscles, which is supplied by the sympathetic nervous system. Thyroid hormones act directly on the skin to cause it to become warm and smooth. It also acts on skeletal muscles to induce a *generalised myopathy* characterised by muscle weakness. The muscle weakness, and increased metabolic rate together account for the sensation of dyspnea so common in

thyrotoxicosis. Thyroid hormones have a variety of effects on the cardiovascular system: they increase the heart rate and reduce the systemic vascular resistance. Both these changes can be accounted for by the increased sensitivity to and probably the increased number of, beta receptors which follows thyrotoxicosis. The thyroid hormone also has direct vasodilatory effects by causing smooth muscle relaxation. The reduction in systemic vascular resistance leads to an increase in stroke volume. This coupled with an increase in heart rate increases cardiac output. This increased blood flow is required to sustain the hypermetabolic state in most organ systems. Clinically, these changes are manifested as a resting tachycardia with a hyperactive apical impulse. The pulse pressure is wide, and a third heart sound may be present on auscultation. A systolic ejection murmur is frequently heard. In older patients particularly, there may be atrial fibrillation, and often the reversal of the thyrotoxic state may revert the patient back to a normal sinus rhythm. Less frequently, there may be a thyrotoxic cardiomyopathy which may manifest with features of cardiac failure, including peripheral edema and pulmonary congestion. Since many of these patients continue to exhibit features of a hyperdynamic circulation, this state is often called a *high output cardiac failure.* Although the cardiac output is higher than is seen in most other patients of cardiac failure it is unable to meet the requirements of the thyrotoxic individual given the hypermetabolic state. In the gastrointestinal tract, thyroid hormones act to increase motility and this usually manifests with hyperdefecation as the main symptom. The thyroid hormone has been shown to increase rates of bone turnover and this may lead to osteoporosis over a period of time. Finally, hyperthyroidism is known to cause changes in behaviour which may manifest as alterations in mood, anxiety, emotional lability and when severe, intellectual dysfunction. Sleep disturbances are sometimes seen as a manifestation of the above problems.

The clinical manifestations of thyrotoxicosis can range from mild to severe, and often patients may complain of symptoms only when specifically questioned. The common clinical manifestations of thyrotoxicosis are detailed below.

In general, the symptoms of sympathetic overactivity such as anxiety and hyperactivity are less common in the older patients than in younger ones with thyrotoxicosis. Some elderly patients have purely cardiovascular complications of thyrotoxicosis such as arrhythmias and cardiac failure, and manifest no signs of sympathetic overactivity. Such patients have been said to have '*apathetic thyrotoxicosis*'.

Biochemical confirmation of thyrotoxicosis is easy to obtain by an elevated FTI or free T_4, and

Clinical manifestations of thyrotoxicosis

Symptoms

Nervousness
Fatigue
Heat intolerance
Tremor
Hyperactivity
Palpitation
Tremor
Weight loss
Increased frequency of bowel movements
Increased appetite
Menstrual disturbances

Signs

Tachycardia
Irregular pulse (atrial fibrillation, and other arrhythmias, sick sinus syndrome)
Increased pulse pressure
High output cardiac failure
Tremor
Eyelid retraction, and lid lag on looking downwards
Warm, moist, smooth skin
Proximal muscle weakness
Other signs specific to cause of thyrotoxicosis e.g. goitre in Graves' disease

elevated T_3 levels. In patients with Graves' disease the T_3 tends to show greater elevations than the T_4. Measurement of the TSH by the newer sensitive assays, would reveal the TSH to be suppressed below the normal range, due to feedback inhibition of pituitary by the high thyroid hormone levels.

In pregnant women with hyperthyroidism, radioactive iodine is contraindicated and antithyroid drugs are the treatment of choice. Propylthiouracil is the preferred agent (if available) since it crosses the placental barrrier poorly. Carbimazole is an acceptable alternative, though its use has been associated with a minor birth defect (aplasia cutis).

Graves' Disease

Graves' disease is associated with hyperthyroidism secondary to the production of an antibody to the receptor for TSH on the thyroid follicular cells. Under normal circumstances, TSH binds to its receptor and stimulates the thyroid gland to make hormone. Patients with Graves' disease produce an abnormal antibody to the TSH receptor. This antibody on binding to the TSH receptor stimulates it in a manner similar to TSH. This leads to effects which would be expected with high circulating TSH, that is, *thyroid growth* and hyperplasia, and *excess thyroid hormone* production. The former manifests as goitre, and the latter as hyperthyroidism, since the antibody production is not under normal feedback inhibition, unlike TSH. Besides thyroid involvement, patients of Graves' disease may also have infiltration of extraocular muscles with lymphocytes, leading to *proptosis* and *ophthalmoplegia.* Less commonly they have involvement of the skin *pretibial myxedema* characterised by mucinous infiltration of the dermis, and *thyroid acropachy* characterised by an appearance of the nails similar to clubbing. All these features of Graves' have a presumed immune basis, though the exact pathogenesis of these is unclear at present.

The TSH receptor antibody in Graves' disease is called *thyroid stimulating immunoglobulin* (TSI) or *thyroid stimulating antibody* (TSAb). The antibody was first discovered in the sera of Graves' disease patients by using guinea pig thyroid tissue. This antibody stimulated the thyroid for a longer time than pituitary TSH and was hence called the *long acting thyroid stimulator* (LATS). This antibody could also be detected in a mouse bioassay system, in about half the patients of Graves' disease. However, due to differences in the structure of the mouse and human TSH receptors, the mouse bioassay could not detect LATS in the other half of the patients. Using a better assay system, where competition between TSH and its receptor antibody (for the TSH receptor) is used, TSH receptor antibodies can be measured satisfactorily in most patients of Graves' disease. They are called *TSH receptor binding immunoglobulins* (TBII). This is because this assay measures all antibodies which compete with TSH for its receptor irrespective of whether they are stimulatory or inhibitory for the receptor. Besides having high levels of stimulating antibodies, some patients of Graves' disease may also have antibodies to the receptor which are inhibitory to its function. The antibodies to the TSH receptor are generally of the IgG class.

It is not known why patients of Graves' disease produce antibodies to their own TSH receptors. We know that for antibody production in response to a peptide, the B cell must get help from a helper T cell. The helper T cell recognises the processed antigen in association with the MHC complex. In many diseases where the immune system is directed against self antigens (autoimmune diseases), certain MHC haplotypes occur more frequently since these are thought to present the processed autoantigen more efficiently. Various studies have shown an association between HLA DR-3 and Graves' disease. It is of interest that though patients of Graves' disease have the

TSH receptor antibody (TSHR Ab), not all people who develop this antibody will develop this disease. The TSHR Ab is seen in patients with subacute and silent thyroiditis, and also in some people exposed to Yersinia infections. The latter group may not even have any evidence of thyroid inflammation. Since B cells interact with T cells in antibody production, and T cell infiltration of the thyroid is seen in patients of Graves' disease, the role for T cells in the development of Graves' disease has been investigated. Abnormalities in subpopulations of the T cell populations have been detected in patients of Graves' disease, but it is not clear if this indeed is the primary defect. Autoimmune thyroid disease runs in specific families; some members in the family may have Graves' disease while others may have Hashimoto's thyroiditis. Monozygotic twins have a 30–60 per cent chance of both getting the disease. This would invoke the additional role of environmental factors in the causation; despite identical genes, there may also be differences in the immune system, as many of the rearrangements and deletions in the immune system occur by poorly understood mechanisms in the early postnatal period.

Clinically, Graves' disease presents with all the features of thyrotoxicosis and a goitre which may be minimally to markedly enlarged. The thyroid enlargement in patients of Graves' disease is smooth, and generally symmetrical. Sometimes a bruit may be heard over the goitre, and this finding is more common in a large goitre. In some patients the goitre may be difficult to detect. Associated features include *ophthalmopathy* characterised by exophthalmos, and in rare cases, chemosis and ophthalmoplegia. Ophthalmoplegia may lead the patient to complain of double vision. It occurs due to the mechanical tethering of the extraocular muscles secondary to inflammation and mucinous deposition which can lead to marked enlargement of these muscles. The enlargement of the muscles, and the deposition of mucinous substance in the limited space of the bony orbit leads to the development of *exophthalmos*. Severe *exophthalmos* can lead to exposure keratitis and corneal ulceration. The optic nerve may be compressed due to the high pressures in the orbit; fortunately this happens only rarely.

Another clinical manifestation of Graves' disease is *pretibial myxedema* which is seen in a minority of patients. This kind of skin involvement gives the appearance of localised area of thickening, which can be quite marked with discolouration in the pretibial region. Thyroid *acropachy* is generally not seen in other forms of thyrotoxicosis. In some patients the terminal part of the nail is lifted up from the nail bed; this is referred to as *Plummer's nail.*

The treatment for Graves' disease involves the use of antithyroid drugs, radioiodine ablation of the gland, or surgical removal of the gland. The choice of the options depends on various factors such as the patient's age, presence of contraindications to one treatment modality or the other, failure of a previously used therapeutic modality and the patient's choice. With all therapies, there is a chance of recurrence. Recurrence rates are more common with antithyroid drug therapy. Radioiodine therapy is popular as this isotope is concentrated selectively in the thyroid gland and destroys the thyroid follicular cells. However, it takes a few months to have effect, and the radioiodine continues to slowly destroy thyroid tissue leading to delayed hypothyroidism. This can be prevented by using lower doses of radioiodine though this admittedly causes a poorer initial response. Some clinicians like to prescribe large doses of radioiodine in the hope of a quick and complete initial response, which the assumption that the almost inevitable hypothyroidism that would follow in later years is easy to treat with replacement thyroid hormone therapy. A more conservative approach is to calculate an exact dose based on the size of the gland and radioiodine uptake of the thyroid gland; though there exist formulae to do this, individual responses to these calculated doses differ greatly

Details of these therapies will be discussed later in the chapter.

Toxic Multinodular Goitre

The pathogenesis of multinodular goitre is largely unknown, but is probably related to the presence of the same stimulus which causes diffuse goitres, that is, prolonged TSH stimulation. It is presumed that this prolonged stimulation causes differential growth of follicles, leading to multinodularity. In keeping with this theory of prolonged stimulation, multinodular goitres occur more often in older people. It is also known that all follicles are able to take up iodine and synthesise thyroid hormone to some extent in the absence of TSH. This is referred to as *autonomy* or *TSH-independent follicular function.* In a multinodular goitre, sometimes generation of a number of autonomous follicles may lead to thyroid hormone production rates in excess of what is required for the individual. In these circumstances the person would become thyrotoxic. A high level of thyroid hormones would suppress pituitary production of TSH, thereby leading to loss of activity of the other follicles, though the most autonomous follicles would continue to function in the absence of TSH. Before the onset of frank hyperthyroidism, there is usually a period of subclinical hyperthyroidism, when the patient has a suppressed TSH with normal serum T_3 and T_4 levels.

Toxic multinodular goitres occur more frequently in the elderly. This population is also the most susceptible to developing cardiac disease without the other manifestations of a thyrotoxic state. Hence, tachycardia, atrial fibrillation, unexplained weight loss and psychiatric features should alert the physician to the possibility of hyperthyroidism in the patient who has a longstanding multinodular goitre.

A serum TSH is the screening test if sensitive assays are available; if it is suppressed, T_3 and T_4 can be measured for confirmation. A radioiodine thyroid scan would show a nodular goitre with patchy uptake of the radionuclide, with the TSH-dependent areas having almost no uptake, whereas the autonomous areas would have uptake (*hot nodules*), despite a suppressed TSH.

The treatment for a toxic nodular goitre is either surgical removal of the toxic nodules by partial thyroidectomy or radioiodine ablation of the toxic nodules, since the isotope is selectively concentrated in the toxic nodules. Antithyroid drugs are not a satisfactory therapy since they will have to be taken for a lifetime and often other autonomous nodules may appear. Cost and compliance problems with drugs are also important considerations in a patient requiring long term therapy.

Autonomous Thyroid Nodule

An *autonomous* thyroid nodule is a discrete nodule which functions independent of TSH control, and produces enough hormone to make a person thyrotoxic and to suppress the TSH.

The distinction from a toxic nodular goitre lies in the fact that the rest of the thyroid tissue is normal. The pathogenesis is probably different from a multinodular goitre, since many of the solitary nodules are monoclonal, that is, derived from a single parent cell. The cells forming the adenoma are abnormal as they function independently of TSH. Some studies have shown these cells to have defective TSH receptors which provide stimulatory intracellular signals in the absence of TSH, while the normal TSH receptor needs TSH to bind to it to provide a similar signal.

These nodules are *warm* or *hot* on a radioiodine scan, and often if the patient is thyrotoxic and the TSH is suppressed, the rest of the gland does not take up any radioiodine. The thyroid hormone levels may be elevated in patients with a toxic nodule, and sometimes the nodule may preferentially secrete T_3 over T_4. At some centres all thyroid nodules may be subjected to a *fine needle aspiration biopsy*

(FNAB) without a prior scan. This is thought to be a more cost-effective way of proceeding with the investigation of a thyroid nodule. In FNAB there is no specific cytologic feature of a toxic thyroid nodule to differentiate it from a non-functioning benign nodule. Both these kinds of nodules would show normal appearing follicular cells, with some colloid.

In a patient who has an autonomously functioning thyroid nodule and is thyrotoxic, ablation of the nodule is desired. This may be accomplished either by surgical removal of the toxic nodule, or by radioiodine therapy. Slightly larger doses of radioiodine may be required as compared to the treatment for Graves' disease as these nodules are more radioresistant. In patients who have a very low TSH and consequently little uptake of radioiodine in the extranodular portion of the thyroid, the incidence of post-radioiodine hypothyroidism is low.

Treatment of thyrotoxicosis

The ideal treatment for a patient of thyrotoxicosis would be to treat the cause. Unfortunately in most patients of this condition, such as those with Graves' disease, toxic multinodular goitre, and solitary toxic nodule, the fundamental abnormality is unclear. Therefore, treatment is directed towards either disrupting synthesis of the thyroid hormone with drugs, destruction of thyroid tissue with radioiodine therapy, or surgical removal of the abnormal tissue. The exact method employed depends partly on the underlying disease, since different conditions respond better to certain therapeutic modalities, and partly on other issues such as patient preferences, prior failure of a particular method, and contraindications in a particular patient to a specific method of treatment.

Antithyroid drugs include two major groups–the thiouracils and the imidazoles. Of the thiouracils, propylthiouracil is the only member in clinical use. Of the imidazoles, the ones used are carbimazole in India and Europe, and methimazole in north America. Carbimazole is metabolised rapidly to methimazole in vivo.

Both these classes of drugs act by a similar mechanism on the thyroid gland. They inhibit the organification of iodine, and coupling of the iodotyrosines to form T_3 and T_4. They may also prevent thyroglobulin synthesis. In addition propylthiouracil also prevents peripheral conversion of T_4 to T_3. These drugs may also have an immunosuppressive effect, which could be beneficial in Graves' disease. Either class of drugs is equally effective and there is not much to choose between the drugs.

Propylthiouracil is more expensive and requires more frequent dosing due to its shorter half-life. The usual dose of propylthiouracil is 200–600 mg/day in three or four divided doses, though doses as high as 900 mg have been used. The dose of carbimazole is 20–40 mg per day in a single or twice daily dose, though higher doses may be needed for Graves' disease as there is a greater likelihood of remission. In other conditions, where treatment may be lifelong there are problems with cost, compliance and breakthrough from drug effects, and a more permanent cure such as radioiodine or surgery is justified. However, in these patients drug therapy is an initial option to control symptoms rapidly and to prepare patients for surgery. For patients receiving radioiodine, initial treatment with drugs serves to deplete the thyroid gland of thyroid hormone, which is useful in preventing the massive release of hormone in the early phase after radioiodine treatment (*radiation thyroiditis*).

Though 90 per cent of patients of Graves' disease respond initially to drugs, permanent remissions are rare. If a patient goes into remission, the drug should be continued for a further period of six months to a year, with the dose being titrated to keep the patient euthyroid. This is thought to increase the duration of remission. Patients will frequently relapse and will need further courses of drugs. If relapses are frequent, or do not respond well to

drugs, radioiodine or surgery should be considered. Patients who do not respond well to drugs, generally have larger goitres, and are more severely hyperthyroid. The major side effects of both classes of drugs include skin rashes, and agranulocytosis (which may be rapid in onset and is not related to the dose of the drug). If agranulocytosis occurs, the drug must be stopped. Frequently the first symptom of agranulocytosis is a sore throat, and the patient should be warned about this.

Iodide itself has an inhibitory effect on thyroid hormone levels, particularly in patients of Graves' disease. Acutely, iodide causes a reduction in organic iodine production in the thyroid, known *Wolff-Chaikoff effect,* and also causes a decrease in release of T_4 and T_3 from the gland. For this reason, oral potassium iodide can be used for short periods in severely thyrotoxic patients to achieve reduction in thyroid hormone levels. It should, however, be understood that after a variable period of time, escape from this iodide effect usually occurs.

Radioiodine is an effective, safe and convenient means of ablating thyroid function. I^{131} is the radioisotope usually used, and is given orally. It is rapidly concentrated in the thyroid follicular cell, which it destroys due to the ionising radiation. The thyroid is the only gland to concentrate this isotope in a major way, and the remainder is excreted by the kidney. Only small amounts are taken up by the salivary glands. Since areas in the thyroid with the most amount of activity, such as hyperfunctioning nodules, would concentrate the highest amount of radioiodine, it is an effective way to ablate them. Within weeks to months after radioiodine treatment, thyroid function begins to normalise. However, radioiodine continues to have residual effect for a few years, with a gradual decline in thyroid function, so that the patient may eventually become hypothyroid. The larger the initial dose, the quicker the therapeutic effect, but also the higher the incidence of eventual hypothyroidism. Most physicians feel that hypothyroidism is an easier problem to deal with, both with respect to cost and compliance with treatment, and also with regard to the amount of monitoring the patient requires.

Radioiodine can be used for treatment of nodular toxic goitres, and Graves' disease which is poorly responsive to drugs. There is some evidence that ophthalmopathy of Graves' may be worsened with radioiodine for poorly understood reasons; so in patients with this complication, surgery may be the preferred option. Because there are no extensive long term data on effects of radioiodine in children and pregnant women, it is not recommended in these groups. However, most evidence to date does not suggest any increase in adverse events even in these two groups.

The surgical treatment of hyperthyroidism due to Graves' disease and toxic multinodular goitre involves a subtotal thyroidectomy. In this procedure the bulk of the gland is removed, leaving a few grams on each side on the posterior aspect to avoid damage to the parathyroids. For solitary toxic nodules, a local resection suffices. Prior to surgery, the patient should be euthyroid, and antithyroid drugs, beta-blockers, and iodides are used for this purpose. Complications of surgery include postoperative hypoparathyroidism, recurrent laryngeal nerve damage, and hemorrhage; but these are rare in the hands of an experienced surgeon.

Thyroid Storm

Thyrotoxic storm is a rare condition, characterised by uncompensated thyrotoxicosis with fever, tachycardia, altered mental status and dehydration. It occurs in a previously poorly controlled patient, with a precipitating cause such as infection, trauma, or surgery. The treatment involves supportive measures such as intravenous fluids, cold sponges, and mild sedation. Specific measures include high doses of antithyroid drugs, which may have to be given

through a nasogastric tube. Iodides block the release of thyroid hormone from the gland and can be given in the form of a supersaturated solution of potassium iodide (SSKI), 5 drops (250 mg) three to four times a day. Sodium Ipodate, more commonly used as an oral contrast agent, acts like iodides on the thyroid gland,. and also prevents peripheral conversion of T_4 to T_3. It is given in a dose of 1 gram daily.

Beta-blockers are the cornerstone of therapy as they block all the catecholamine-potentiated effects of thyroid hormone. Propranolol can be given intravenously at a dose of 2–5 mg every four hours. Glucocorticoids are useful in stabilising the circulation and also in preventing the conversion of T_4 to T_3. Dexamethasone 4–6 mg every 6 hours can be given for this purpose. Further details are given in the section on endocrine emergencies (16.11).

HYPOTHYROIDISM

Hypothyroidism is a common disorder of thyroid function, which manifests with typical clinical features irrespective of the underlying cause. Often the onset of this disorder is indolent. For this reason, the diagnosis is often missed, particularly if the symptoms are not severe. In general, it is more obvious if the symptoms develop rapidly, and in patients who are older.

Hypothyroidism can be classified as *primary* if it involves an abnormality of the thyroid gland itself, or *secondary,* if it is due to deficiency in TSH secretion (as in pituitary or hypothalamic disease). Causes of primary hypothyroidism include destruction of thyroid tissue by processes such as thyroiditis, radiation, surgery, or infiltration of the thyroid by tumour or amyloid. Other causes of primary hypothyroidism are iodine deficiency (as in endemic goitre), and more rarely, iodine excess or inherited deficiencies of the enzymes involved in thyroid hormone biosynthesis.

Patients with hypothyroidism complain of a generalised slowing with fatigue, lethargy, and cold intolerance. They may also exhibit weight gain despite decreased appetite, and complain of constipation. The speech is slow and the voice may be hoarse. The patient has bradycardia, and heart sounds may be distant due to a pericardial effusion. The skin is dry and coarse, and there may be non-pitting edema (myxedema). Female patients have menstrual abnormalities including both menorrhagia and amenorrhea. The neurological examination may reveal generalised muscle weakness and a slow relaxation phase of the deep tendon reflexes. In rare cases, cerebellar ataxia may be observed. The patient may be depressed and in more severe cases may have mental impairment with loss of memory and hallucinations. In older persons a diagnosis of dementia can mistakenly be made if hypothyroidism is not excluded.

The laboratory diagnosis is made by the demonstration of an elevated TSH level in patients of primary hypothyroidism. This is a more sensitive indicator than the serum levels of thyroid hormone, which are low. In patients with secondary hypothyroidism, the TSH levels are low, and thyroid hormone levels have to be relied upon for a diagnosis. Thyroid antibody levels, and the radioiodine scan help to define the underlying etiology.

Though most of the effects of hypothyroidism are reversible with the initiation of thyroid hormone therapy, in infants the mental and physical retardation which occurs in the absence of thyroid hormone are irreversible. Immediate replacement of thyroid hormone therapy should therefore be instituted in newborns and infants with this disorder. In most of the developed world it is a common practice to include thyroid hormone screening, in the panel of screening tests performed routinely at birth. Thyroid studies are also a part of the investigations in a child with short stature of unknown etiology.

Endemic Goitre and Cretinism

The only confirmed role of iodine in the human body is in the synthesis of thyroid hormones; deficiency of iodine impairs hormone production. The daily recommended dietary intake of iodine is estimated to be 100–150 μg/day for adults (including lactating and pregnant women). For children below 10 years, 60–100 μg/day may suffice. When the physiologic requirements of iodine in a given population are not met, a series of functional and developmental abnormalities occur, secondary to abnormalities in thyroid function. When iodine deficiency is severe, endemic goitre and cretinism are observed, along with decreased fertility rates and increased perinatal and infant mortality rates. As mentioned earlier, endemic goitre is a part of a series of adaptive processes which occur in the face of iodine deficiency. Low iodine intake causes a rise in TSH in an attempt to increase efficient trapping of available iodine by the thyroid. Prolonged thyrotropin stimulation leads to increase in thyroid size and clinical goitre. The geographical areas affected by iodine deficiency are those which are mountainous, or regions which were covered by glaciers in the past. The melting of snow presumably leached the iodine in the soil. The entire Himalayan region and the northern plains in India are iodine deficient areas. Other iodine deficient pockets in the country include hilly regions in Rajasthan, Madhya Pradesh, the Chota Nagpur plateau, and the Narmada valley in Gujarat. The cities of Delhi and Bombay also have populations deficient in iodine.

The iodine content of most foodstuffs is generally low. This is more so for locally grown foods in iodine deficient areas. Fish, and to a lesser extent meat, eggs and milk, have appreciable amounts of iodine. Hence, iodine deficiency has generally to be treated with iodine supplementation, either in cooking salt, edible oils, or in drinking water. Iodine deficiency can be prevented with appropriate iodine supplementation, but continues to occur due to the failure of programmes for supplementation secondary to socioeconomic and other reasons.

Though iodine deficiency is the commonest cause of endemic goitre in India and most other countries, this disease is found in other regions with adequate iodine intake. This is due to the presence of factors in the diet known as goitrogens, which prevent the organification of iodide by the thyroid. Such factors are found in vegetables of the genus Brassica (such as cabbage). Some foods produce cyanides in the body, which is detoxified by conversion to thiocyanate, which is also a powerful goitrogen. Such foods include cassava, maize, sweet potatoes and lima beans.

A thyroid gland which has lateral lobes with a volume greater than the terminal phalanges of the thumb is considered goitrous. For public health studies conducted in the field, the severity of the goitre can be staged as follows:

Stage 0: no goitre

Stage 1a: goitre detectable only by palpation, but not visible with neck extended

Stage 1b: goitre palpable and visible only when the neck is fully extended

Stage 2: goitre visible with neck in normal position (palpation not needed for diagnosis)

Stage 3: large goitre which can be recognised at a considerable distance

An area is defined as endemic with respect to goitre if more than 10 per cent of children in the age group of children 6–12 years are found to be goitrous. In endemic areas the goitre prevalence is highest in puberty and in early adulthood, and is greater in women. A decline in goitre is seen with age in both sexes.

Thyroid function tests in populations affected by endemic goitre show a high TSH with a low normal T_4, and a normal T_3. These subjects are said to have compensated for subclinical hypothyroidism. Less commonly, patients have frankly low T_4 levels. The I^{131} uptake by the thyroid gland is elevated, as this gland is deprived of iodine and is under strong TSH

stimulation. Longstanding goitres frequently become nodular, presumably due to the differential responsiveness of follicles to TSH stimulation. Some nodules may eventually become autonomous, that is, despite withdrawal of TSH they continue to function, take up large amounts of iodine and produce thyroid hormone. These show up as 'hot' areas or areas of increased uptake on the I^{131} scan. Other nodules are 'cold' and fail to take up radioiodine in spite of TSH stimulation.

Despite being a preventable problem, iodine deficiency continues to occur. In India about 150 million people are estimated to be at risk. Since thyroid hormone is important in brain development, hypothyroidism should be treated as early after birth as possible. In goitrous areas it is essential to test every newborn for congenital hypothyroidism. Methods are available to screen for TSH and thyroid hormone levels on a drop of heel pad or cord blood which can be taken on a piece of filter paper at birth, and then transported to the laboratory. Infants who are hypothyroid should be treated with immediate institution of hormone replacement. Such screening programmes should be carried out in association with programmes designed to supplement iodine in the community. In the sub-Himalayan region, screening studies have reported an incidence of congenital hypothyroidism of 4.2 per cent. This is much higher than the incidence of 1 in 3000 seen in non-endemic areas. There is also some evidence to show that in areas of iodine deficiency, besides an increase in goitrous hypothyroidism, there is an increased rate of thyroid dysgenesis leading to increased frequency of non-goitrous hypothyroidism. This observation suggests that availability of iodine in fetal life is essential for normal thyroid development.

The economic costs of iodine deficiency should not be underestimated. Besides the obviously apparent cases of severe mental abnormality, there is evidence to suggest that mild mental abnormality and sensorineural deafness are more common in iodine deficient populations than previously appreciated. The government of India launched a programme of iodine supplementation in iodine deficiency areas under the National Goitre Control Programme almost three decades ago. However, a review of this programme two decades later indicated a total failure in implementation. The Universal Iodisation Programme was then initiated in 1986, following renewed interest in this problem. The implementation of this programme is being vigorously pursued by both governmental and non-governmental agencies, through the iodisation of edible salt.

Iodine excess is an uncommon problem. Nevertheless, it is known to cause hypothyroidism in susceptible individuals. On the other hand, excess of iodine may also cause hyperthyroidism, especially in people with underlying nodular thyroid disease.

Autoimmune Thyroiditis

Autoimmune thyroiditis includes a group of thyroid diseases in which autoimmune phenomena are responsible for thyroid dysfunction. These different conditions have distinct clinical features, laboratory abnormalities, and pathologic features, but have some features in common. The most common disorder in this group is *chronic lymphocytic thyroiditis,* also known as *Hashimoto's thyroiditis.* The other conditions in this group are postpartum thyroiditis, silent thyroiditis, and atrophic thyroiditis with hypothyroidism. Graves' disease, also of an autoimmune etiology, is sufficiently distinct from the disorders included in this group, mainly due to the presence of hyperthyroidism secondary to thyroid stimulating antibodies. For this reason, it is not included in this group of disorders, all of which lead to decreased function of the thyroid gland. Autoimmune thyroid diseases and Graves' disease seem to co-exist in certain families. In rare cases, the same person may

show features of different forms of autoimmune thyroiditis at different times during the course of their illness. Uncommonly, features of Graves' disease can occur in a patient with previous Hashimoto's thyroiditis, and when this occurs it is given the name Hashitoxicosis by some. However, periods of thyrotoxicosis may occur in patients of Hashimoto's thyroiditis and other autoimmune thyroiditis due to the release of preformed hormone from the gland secondary to massive destruction of the gland by the acute lymphocytic infiltrate. Such episodes of thyrotoxicosis are probably more common and should be differentiated from the true hyperthyroidism seen in the entity of Hashitoxicosis.

In this section, Hashimoto's thyroiditis will be dealt with since it is the commonest and best described variant of autoimmune thyroiditis. Of the others, silent thyroiditis will be dealt with in some detail later in the chapter.

Hashimoto's thyroiditis is named after the Japanese physician who first described this condition in 1912. This condition is characterised by a goitre, and its histology shows diffuse lymphocytic infiltration with fibrosis and areas of either hyperplasia or atrophy of follicular cells. Some cells have an eosinophilic cytoplasm and are called *Hurthle cells*. The lymphocytic infiltrate may be severe, and sometimes lymphocytes may form germinal centres in the thyroid. The identity of the autoantigen in the thyroid against which these lymphocytes are directed is unclear but thyroglobulin and thyroid peroxidase are two of the candidate antigens against which antibodies can be detected in this condition. As mentioned earlier, this lymphocytic infiltrate may cause no clinical abnormalities except for a goitre. As the disease advances, hypothyroidism eventually supervenes. Some studies indicate that only 10 per cent of euthyroid patients with a goitre and positive thyroid antibodies eventually become hypothyroid. However, once subclinical hypothyroidism develops the progression to frank hypothyroidism seems more likely. Subclinical hypothyroidism is defined as the stage where the TSH is elevated, while the thyroid hormone levels remain in the normal range. Some patients may have pressure symptoms from the goitre, which is generally symmetric but may be variably enlarged. The thyroid enlargement is generally nontender and firm, and may sometimes have an irregular surface, making it difficult to clinically distinguish it from a multinodular goitre.

The diagnosis is usually easy in a patient with goitre and positive antithyroid antibodies. The antithyroid peroxidase antibody is more sensitive for the disease than the antithyroglobulin antibody. Sometimes the diagnosis is made on a surgical specimen on the basis of the pathology. If antibody studies are unavailable, FNAB may be helpful if it shows a large number of lymphocytes, plasma cells and Hurthle cells in a patient with a goitre.

There is no satisfactory treatment to halt the autoimmune process in thyroiditis. In hypothyroid patients thyroxine treatment is indicated. In patients who have a goitre, but are euthyroid, some physicians use thyroxine replacement in an attempt to reduce TSH production and to make the gland quiescent. The degree of regression of the goitre with such treatment is variable, so that the patient needs to be carefully monitored.

Subacute Thyroiditis

Subacute thyroiditis is painful inflammation of the thyroid gland. It is presumed to be of a viral origin as it is seen most often during summer months, often preceded by a respiratory infection. Antibodies to a variety of viruses have been found in different studies. The observation that this disease is more common in people with the HLA-Bw35 subtype may be due to the fact that this haplotype allows viruses to cause a T cell response directed against thyroid tissue.

Subacute thyroiditis is uncommon in the Indian subcontinent, and occurs widely in North America, Europe, Scandinavia, and Japan. It is

known by various names including *granulomatous thyroiditis,* and *De Quervain's thyroiditis.*

Patients usually present with neck pain, with an enlarged tender thyroid. The thyroid inflammation may lead to a release of thyroid hormone secondary to destruction of thyroid cells. This leads to periods of thyrotoxicosis. However, at this time the patient has a low radioiodine uptake, since the thyroid gland is not functioning normally. This low uptake distinguishes this form of 'destructive thyrotoxicosis' from that caused by hyperthyroidism (as seen in Graves' disease, and toxic nodular goitres). Besides this, the patient may also have symptoms of generalised malaise and bodyaches, as seen in other viral illnesses. Sometimes, the patient may even be febrile.

In most patients the illness lasts for 2–4 months. The thyrotoxicosis resolves in 4–10 weeks, since it is due to release of preformed hormone. As the gland does not function normally, in cases with a prolonged course, there is a period of hypothyroidism following the thyrotoxic phase. As the patient recovers, the follicles regenerate, and normal thyroid function is restored.

Besides the characteristic feature of severe pain in the thyroid region, another feature of this disease is the very high erythrocyte sedimentation rate (ESR). The ESR is often above 100 mm/hour. In the absence of pain and a high ESR, the diagnosis of subacute thyroiditis should be reconsidered. The other cause of painful thyroid enlargement which must always be excluded is suppurative thyroiditis, in which thyroid tenderness is localised, and local signs of inflammation such as redness and warmth may be present. Fever may be more prominent in suppurative thyroiditis, and this disease occurs rarely in immunocompetent patients. Other causes of pain in the thyroid are hemorrhage into a thyroid nodule, and a rapidly growing anaplastic carcinoma of the thyroid; these disorders can be recognised by history and physical findings.

The most effective therapy for subacute thyroiditis is corticosteroids. Aspirin can also be used. Both agents act by reducing inflammation and need to be given for about four weeks.

Silent Thyroiditis

Silent or painless thyroiditis differs from subacute thyroiditis, as there is no pain and the etiology is presumed to be autoimmune rather than infectious. Like subacute thyroiditis, it is characterised by thyroidal destruction, though the pathology is different since there is no granuloma formation, and lymphocytic infiltration is prominent. A similar disorder occurring in the postpartum period, is called *postpartum thyroiditis;* it is probably a variant of silent thyroiditis.

The presentation of silent thyroiditis is variable. Patients may present in the phase of 'destructive thyrotoxicosis' with symptoms of thyrotoxicosis and thyroid enlargement. Some patients may present at a later stage when hypothyroidism occurs. Laboratory tests would reflect high thyroid hormone levels with a low radioidine uptake in the former group, and low thyroid hormone levels are seen in the hypothyroid group. As the thyroid regenerates, radioidine uptake in the thyroid increases. Sometimes the disease has a prolonged course and the patient may remain hypothyroid for prolonged periods of time. Over half the patients have antibodies to various thyroid antigens. Some patients who seem to have typical Hashimoto's thyroiditis otherwise, may in fact have periods of thyrotoxicosis, and other features to suggest episodes of silent thyroiditis. It is possible that a significant proportion of patients with silent thyroiditis are not diagnosed due to a lack of specific symptoms. Some of these patients who present in the initial thyrotoxic phase with goitre are mistakenly thought to have Graves' disease. However, as pointed out earlier, they would have a low radioidine uptake, and would not have the eye signs and dermopathy of Graves' disease.

Silent thyroiditis should also be differentiated from other disorders causing thyrotoxicosis with a low radioiodine uptake. These include iodine-induced thyrotoxicosis which can occur following a iodine load in patients of pre-existing thyroid disease (such as Graves' disease and multinodular goitre). Exogenous intake of thyroid hormone is also a cause of thyrotoxicosis with a low radioiodine uptake. *Struma ovarii* is a very rare condition in which the thyroid hormone is produced ectopically in an ovarian tumour, leading to thyrotoxicosis and low uptake of radioiodine in the thyroid gland, as most of the iodine is taken up by the pelvic mass.

Since silent thyroiditis is self-limiting, no treatment is usually needed. Antithyroid drugs are not helpful in the thyrotoxic phase as the thyroid hormone release is secondary to thyroid tissue destruction and antithyroid drugs would have no effect on this. In patients with prolonged symptomatic hypothyroidism, thyroid hormone replacement may be an option till recovery of thyroid function.

Other causes of hypothyroidism

Uncommon causes of primary hypothyroidism include thyroid agenesis, or dysgenesis and metabolic defects leading to abnormalities of thyroid hormone biosynthesis. In the latter case, there may be a positive family history.

Pituitary abnormalities such as a tumour or 'apoplexy' may lead to secondary hypothyroidism due to reduction in TSH secretion. This generally occurs in association with other pituitary hormone deficiencies, and the thyroid gland is small or impalpable.

Treatment The treatment of hypothyroidism should be directed at its cause, but often this is not possible. In most cases replacement with T_4 is the method of choice. T_4 used to be extracted from animal thyroid, but is now manufactured synthetically. It is cheap, relatively stable and is absorbed well orally. It has a long half-life of about a week, and can be given once daily. Since it takes four to five half-lives for a drug to reach steady state levels, one has to wait a month before steady levels of serum T_4 are achieved. Though T_3 is the active hormone, it need not be taken since the T_4 can be converted in the body to T_3. However, in some situations such as myxedema coma, where a rapidly acting drug is required T_3 may be used. If available, a sensitive TSH assay is the method of choice to monitor thyroid hormone replacement therapy for patients with primary thyroid disease. In patients with secondary hypothyroidism due to pituitary disease a TSH measurement is not useful; a serum T_4 level provides a guide to the adequacy of replacement. Usual replacement doses of T_4 range from 0.1 mg to 0.15 mg/day. In the elderly and in those with heart disease, a much lower starting dose should be used, and increased gradually.

Myxedema coma

Myxedema coma is a rare manifestation of severe untreated hypothyroidism. It is characterised by unconsciousness and hypothermia, in association with other features of hypothyroidism. This state may be precipitated in a patient of hypothyroidism due to an infection, other acute illnesses, exposure to cold, or by the use of sedatives. If the clinical picture of severe hypothyroidism is convincing, treatment should be initiated immediately without awaiting laboratory confirmation of the diagnosis. T_4 is converted rapidly in vivo to T_3 and is adequate for this purpose in most patients. It can be given intravenously or through a nasogastric tube in an initial single dose of 0.3 mg. Subsequently, the patients can be maintained on the usual daily maintenance dose. Some clinicians like to add a small dose of T_3 in the belief that in severe sickness, the conversion of T_4 to T_3 in vivo is impaired (see section on sick euthyroid syndrome). A dose of T_3 of 10 micrograms every 8 hours is usually adequate. The disadvantages of T_3 are a higher incidence of cardiovascular side effects, and its availability only in an oral form.

Patients of hypothyroidism may have coexisting adrenal insufficiency particularly if

they have underlying pituitary disease or chronic lymphocytic thyroiditis. In the former group, this occurs due to coexistent corticotropin (ACTH) deficiency, and in the latter it occurs due to associated autoimmune adrenal destruction. Since thyroid hormone replacement causes an increase in glucocorticoid turnover, patients must also simultaneously be supplied with glucocorticoids if there is a possibility of adrenal insufficiency (to prevent the development of an adrenal crisis). The usual dose for this is hydrocortisone 100 mg every 8 hours intravenously.

Myxedema is frequently associated with retention of free water and low serum sodium concentration. If severe, this may contribute to the mental impairment. Fluid restriction and, in rare cases, small volumes of hypertonic saline may be used to corrrect this. Hypothermia is treated by gradual rewarming with blankets. Other supportive measures may be needed to maintain adequate circulation and ventilation.

SICK EUTHYROID SYNDROME

Virtually all severe illness such as trauma, sepsis, malignancy, febrile illnesses and even undernutrition, cause changes in thyroid hormone concentrations in people who have no apparent thyroid disease. Most commonly, the T_3 is low as there is reduced peripheral conversion of T_4 to T_3.

In more severe illness, there is a reduction in circulating TSH, and both T_4 and T_3 levels are low. It is interesting that even though the total T_4 levels are low in these patients the T_3 resin uptake is seen to be high. This is because there are factors in the serum of these patients which prevent the binding of thyroid hormone to TBG, and so a high proportion gets bound to resin. The levels of rT_3, which is the inactive metabolite of T_4, are high due to its reduced clearance in sickness. The mechanism for these changes is not certain, but they are believed to be mediated by cytokines acting on the thyroid and pituitary gland. The low levels of thyroid hormone in illness seem to reduce metabolic rate and protein catabolism, and this may be an adaptive phenomenon. Studies have shown that the administration of thyroid hormones to these ill patients does not improve prognosis and may actually worsen it.

In the hospitalised patient who is ill, effects of drugs on thyroid hormone metabolism must always be considered, before attributing these changes to the 'sick euthyroid state'. Corticosteroids and dopamine are known to reduce TSH levels. Propranolol prevents conversion of T_4 to T_3. Iodine containing drugs such as amiodarone can cause both hypothyroid and hyperthyroid states.

MULTINODULAR GOITRE

A non-toxic multinodular goitre is a slowly developing nodular enlargement of the thyroid resulting from an excessive replication of thyroid epithelial cells which is not uniform in all areas of the gland. In some of these cases, it is presumed that initially the excess proliferation of the thyroid epithelial cells is uniform, and leads to a diffuse simple goitre, but with the passage of time, different regions proliferate at different rates leading to a nodular architecture with a large number of follicles (which vary greatly in size and cellular morphology). The reason for this enlargement of the thyroid gland is not always clear. In regions of iodine deficiency goitre occurs due to the high levels of TSH which drive follicular proliferation. As mentioned earlier, prolonged periods of TSH stimulation may induce a differential response of follicular cells and may eventually lead to multinodular goitres. However, multinodular goitres are very common in areas with no iodine deficiency, and most of these cases are associated with normal TSH levels. The pathogenesis of the goitre is not clear in these cases. It is possible that these cases are due to a tendency of the thyroid epithelial cells to proliferate in an uncontrolled manner

due to an abnormal sensitivity to certain growth factors, one of which may be TSH.

The symptoms of a non-toxic multinodular goitre are related to the presence of an enlarged thyroid, and may be of a purely cosmetic nature, or related to pressure symptoms caused by a large gland. When severe, pressure symptoms may lead to compression of structures in the thoracic inlet. Physical examination generally reveals a nodular feel of the thyroid on palpation, and the asymmetric nature of the gland is often noted on inspection. Rarely, the nodular nature or thyroidal origin of the mass cannot be appreciated, and ultrasonography or a radioiodine scan may be needed to establish the diagnosis. The latter would delineate nodules with early autonomy, by showing them as 'hot' areas with 'cool' surroundings. In the group of patients with autonomic nodules, who are clinically and biochemically euthyroid, subclinical hyperthyroidism is detected by a suppressed TSH level in a sensitive TSH assay, despite the normal thyroid hormone levels. The scan would also reveal any large cold areas which may need to be followed up for thyroid cancer.

If the gland is not very large, and specially if the TSH is high, treatment should be attempted with thyroid hormone replacement. This will act to reduce TSH levels, and since this is a growth factor for the thyroid, which may lead to some regression of the goitre. In patients with large goitres with compressive symptoms, or with cold areas suspicious of malignancy, and in those patients who have autonomous nodules, surgical therapy is the treatment modality of choice.

THYROID CANCER

Thyroid cancer is a rare disease. It is relatively slow-growing, and generally has favourable cure rates. The only factor definitely implicated in thyroid cancer is radiation exposure. However, many patients of thyroid cancer have not known radiation exposure. The incidence of thyroid cancer is increasing in most countries due to better detection. Most thyroid cancers are detected during the evaluation of thyroid nodules. Many centres routinely perform FNAB in all patients with thyroid nodules (Fig 16.16). In most cases a needle aspirate yields a firm diagnosis of a benign or malignant nodule. Sometimes the aspirate may show a hypercellular aspirate with little or no colloid, though the individual cells have no characteristics of malignant cells. Such aspirates are seen with benign or malignant follicular neoplasms, and the only evidence for malignancy in these tumours is found on tissue sections where features of vascular and capsular invasion may be seen. Such patients may be referred for surgery or evaluated further with a radioiodine scan. In patients who have a radioiodine scan for the evaluation of a thyroid nodule, a cold nodule should always be viewed with suspicion, since 10–20 per cent of these may harbour thyroid cancers. This is because thyroid cancer cells are less differentiated as compared to normal thyroid epithelial cells and cannot concentrate iodine. Other causes of a cold nodule at scan are a benign thyroid adenoma, bleeding into a thyroid nodule and a thyroid cyst. A functioning thyroid nodule is almost never malignant.

Clinical features which should alert one to the possibility of a malignant thyroid nodule are a rapidly enlarging nodule, a hard and fixed nodule, associated vocal cord paralysis due to invasion of the recurrent laryngeal nerve, or associated lymph node enlargement with the nodule.

The characteristics of a malignant thyroid nodule are :

1. rapid enlargement
2. hard, fixed nature
3. the presence of hoarseness with vocal cord paralysis
4. the development of a nodule in a person < 14 years or > 65 years
5. the presence of ipsilateral lymphadenopathy
6. a history of ionising radiation
7. evidence of hypofunction as seen in radioiodine scan
8. suspicious or malignant as seen with fine needle biopsy

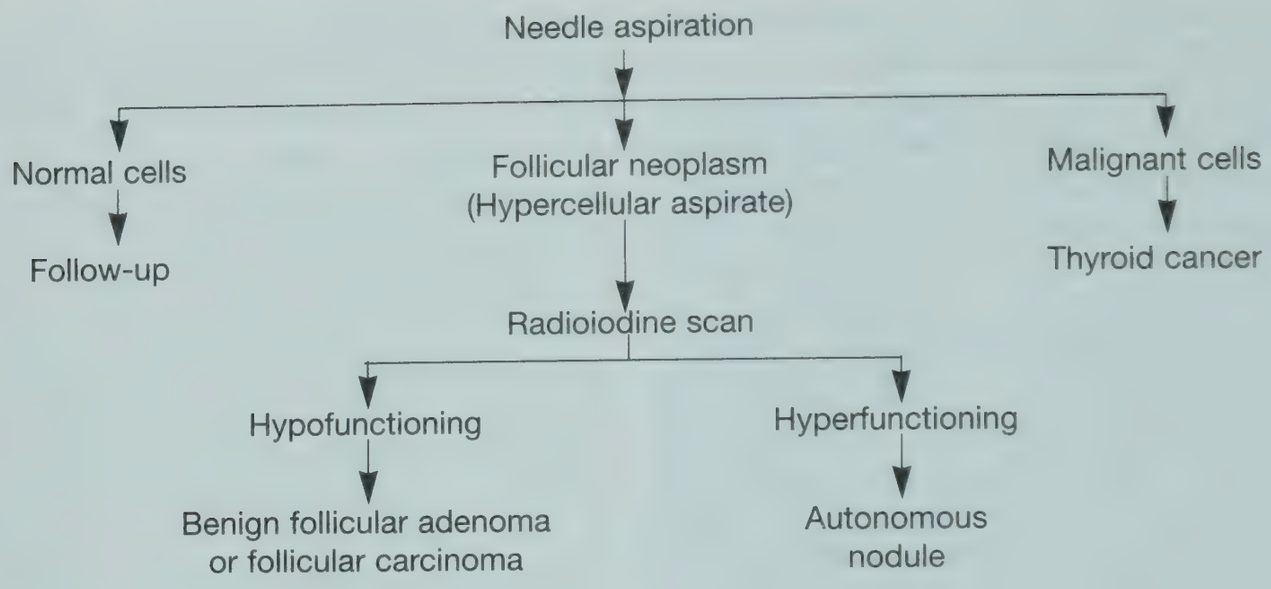


Fig 16.16 Evaluation of a solitary thyroid nodule

FNAB is the investigation of choice, and in the hands of an experienced operator in conjunction with an experienced pathologist, has low false-negative and false-positive rates. The pathology of thyroid cancers is most commonly described as *follicular* or *papillary,* depending on the arrangement of the cells. There are also some differences in clinical behaviour in the two tumour types. Less commonly a very aggressive form of undifferentiated tumour of the thyroid is seen, and this is known as *anaplastic* carcinoma. A cancer may arise in the thyroid from cells other than the thyroid epithelium, and when the cell of origin is the C cell (or calcitonin-producing cell) this is known as a *medullary* carcinoma. Medullary carcinomas generally arise as a part of a syndrome of multiple tumours of the endocrine organs, known as the Multiple Endocrine Neoplasia (MEN) syndrome. Metastatic cancer of the thyroid is uncommon. Also, the thyroid may be the site for a primary lymphoma in rare cases.

Papillary carcinomas are the commonest type of thyroid neoplasms. Frequently there are small foci of this tumour, and are discovered incidentally at thyroidectomy performed for other reasons. Many of these tumours probably never become apparent during a person's lifetime and may be discovered at autopsy. However, some tumours are quite aggressive, and have significant spread at the time of diagnosis. Papillary cancers tend to spread early to the draining lymph nodes, but complete excision of the tumour and involved lymph nodes leads to a cure. Spread to regional lymph nodes is not a poor prognostic sign, if these lymph nodes are removed at surgery. However, spread to lungs, bone and other distant organs occurs late and is a poor prognostic sign. A common variant of papillary cancer is the *follicular variant,* where the malignant epithelial cells form follicles. This kind of papillary cancer can be distinguished from a true follicular cancer by the characteristic nuclear features of papillary cancer and the observation of areas of papillary growth in the tumour. The cells in papillary cancers show clearing of the nucleus with a characteristic grooving of the nuclear membrane.

A *follicular cancer* of the thyroid occurs in less than 10 per cent of thyroid cancers. In an FNAB it may be difficult to distinguish a well-differentiated follicular cancer from a benign follicular adenoma, since the aspirated cells may look similar. In the surgically resected specimen, the distinction can be made on the basis of extracapsular spread, vascular invasion, and the other cellular features of malignant neoplasia.

Follicular cancers tend to metastasise more frequently via the blood vessels to distant tissues. Nevertheless their growth, like most thyroid cancers, is slow; if they are resected early, the prognosis is good.

Sometimes the cells in both papillary and follicular cancers are poorly differentiated. These cells may sometimes be arranged in solid islands, and frequently normal thyroid architecture is completely lost. This is called the *insular variant*. These tumours tend to have a poorer prognosis and grow and spread fast. Even more rarely, the cells are completely bizzare-looking and spindle-shaped and there is difficulty in determining the origin of the malignant cells; such cancers are the *anaplastic variants*, and have a very poor survival. Sometimes the follicular epithelial cells in a thyroid cancer become granular and eosinophilic; this is called a *Hurthle cell variant*. These eosinophilic Hurthle cells are also seen in benign conditions such as Hashimoto's thyroiditis.

A *medullary cancer* of the thyroid is rare and arises from the calcitonin-secreting C cell. It is more malignant than the well-differentiated cancers of the follicular epithelium and shows early spread to the lymph nodes. Younger patients with this condition should be screened for the multiple endocrine neoplasia syndrome (type 2), as they may have coexisting parathyroid and adrenal tumours.

Classification of thyroid cancers

A. Thyroid cancers arising from follicular epithelium
- Well differentiated papillary and the follicular variant of papillary cancer
- Well differentiated follicular cancer
- Poorly differentiated thyroid cancer including insular variant
- Anaplastic thyroid cancer
- Hurthle cell or oxyphilic variant

Cancer arising from C cells
- Medullary thyroid cancer

B. Cancer arising from other cells
- Thyroid lymphoma
- Metastatic thyroid cancer

The treatment of thyroid cancers is by total thyroidectomy. An attempt is made to retain parathyroid glands, and to avoid damage to the recurrent laryngeal nerve. After surgical removal, radioiodine may be given to ablate any residual thyroid tissue. The patient will need to be started on thyroid hormone replacement for the rest of her life, and this will also serve to supress the TSH (which is a growth factor for thyroid epithelial cells). The serum thyroglobulin is a good marker for recurrent disease, as this protein is only produced by thyroid cells. The patient should be followed-up at regular intervals to look for evidence of local or distant recurrence.

KEY CONCEPTS

Thyroid function tests

- Serum T_4 measures both bound (99.9%) and free (0.1%) T_4. It is increased in thyrotoxicosis and reduced in hypothyroidism. When TBG is increased (e.g., estrogen intake, pregnancy, liver disease), T_4 is increased but free T_4 is normal.
- T_3 resin uptake is a test in which the patient's serum is incubated with labelled T_3 and resin. The proportion of labelled T_3 which binds to the resin is a measure of the unoccupied binding sites (for T_3) on the patient's TBG. Thus, in hyperthyroidism T_3 resin uptake is increased.
- The free T_4 index combines T_4 and T_3 resin uptake to produce a measure of thyroid function which is independent of TBG variation.
- Serum TSH is a very sensitive test of hypothyroidism (levels are elevated). Hyperthyroidism leads to suppression of TSH levels.
- RAIU at 24 hours (after administration of isotope) is generally increased in hyperthyroidism. RAIU is decreased if hyperthyroidism is due to an extrathyroidal source of T_3/T_4 or thyroiditis.

Thyrotoxicosis

- The most common cause in India is a toxic multinodular goitre, while in North America and Europe it

is most often autoimmune in origin (Graves' disease). Other causes include thyroid adenoma, thyroiditis and exogenous administration of thyroid hormone.

➢ Clinical manifestations are related to increased BMR and signs of adrenergic hyperactivity. Symptoms include weight loss in the face of an increased appetite, increased sweating, heat intolerance, diarrhea, and palpitations. Clinical signs include tachycardia, stare, lid lag, goitre (often with a bruit) and a warm, moist skin. Graves' disease is associated with an infiltrative ophthalmopathy, pretibial myxedema and thyroid acropachy. Apathetic thyrotoxicosis is a form seen in the elderly when cardiac manifestations predominate (atrial arrhythmias and CHF). Elevated T_3 or T_4 in the presence of undetectable TSH readily suggests the diagnosis. A radioiodine scan may help identify a toxic nodule. RAIU is elevated (except in thyroiditis and exogenous intake). Therapeutic options include antithyroid drugs (complete remission in <50%). Surgery (preferred for MNG with compressive symptoms) or radioiodine ablation (preferred in the elderly; risk of hypothyroidism increases with time) may be performed when the patient is euthyroid.

➢ Thyroid storm is a sudden exacerbation of symptoms and signs of thyrotoxicosis which may progress to coma. It is treated with KI, dexamethasone, carbimazole, beta-blockers and proper fluid replacement.

Hypothyroidism

➢ Worldwide, the most common cause of hypothyroidism is iodine deficiency; in Europe and North America it is autoimmune thyroiditis. Other causes include dyshormonogenesis, post-thyroidectomy, post-radioiodine ablation, and hypopituitarism.

➢ Symptoms of hypothyroidism include weight gain, lethargy, cold intolerance, constipation, menorrhagia and slowing of mentation. Clinical signs include bradycardia, hoarseness of voice, loss of a lateral third of the eyebrows, cold, dry skin, macroglossia and slowing of the relaxation phase of the deep tendon reflexes. In hypothyroidism of pituitary origin (secondary hypothyroidism), amenorrhea is common (instead of menorrhagia) and the hair and skin are dry but not coarse.

➢ Most patients with hypothyroidism have low T_4 levels but elevated TSH levels; in secondary hypothyroidism, both and T_4 TSH levels are low. Additional laboratory findings include hyponatremia, hypercholesterolemia and a low voltage ECG. Thyroid antibodies are present in patients with autoimmune hypothyroidism.

➢ Treatment consists of thyroxine replacement to achieve free T_4 level at the upper limit of normal and TSH level in the normal range. Smaller doses are used in elderly patients initially and in those with cardiovascular disease or a severe degree of deficiency.

➢ Myxedema coma is a condition associated with severe hypothyroidism which additionally manifests with hypothermia, hypoglycemia and coma. Treatment is with intravenous T_4, cortisol and fluid replacement.

Endemic goitre

➢ In the Himalayan and sub-Himalayan regions of India, iodine deficiency results in an adaptive goitrous response from the thyroid gland due to prolonged TSH stimulation. An area is described as endemic (for goitre) if >10% of the children between 6–12 years have a goitre.

➢ Endemic goitre is associated with low-normal concentrations of T_4, normal T_3 levels but with elevated TSH levels. Endemic goitres are often nodular in character. Some of the nodules may become autonomous (with resultant thyrotoxicosis). There is an association of endemic goitre with mild mental abnormality and with sensorineural deafness.

➢ Important preventive measures include neonatal screening for hypothyroidism and supplementation of dietary salt with iodine.

Hashimoto's thyroiditis

➢ This is an autoimmune condition characterised histologically by chronic inflammation and lymphocytic infiltration of the thyroid. The clinical significance lies in that it can cause hypothyroidism (in over 20%) and may be associated with other autoimmune diseases.

➢ Clinically, women are more often affected and the hallmark is a non-tender, rubbery, smooth enlargement of the thyroid gland.

➢ Serum levels of antimicrosomal antibodies (thyroid peroxidase) and antithyroglobulin antibodies may be elevated.

➢ Once hypothyroidism occurs, treatment is with thyroid hormone replacement.

Thyroid cancer

➢ Thyroid cancer may be papillary (60%; affects all ages; undergoes lymphatic spread), follicular (20%; affects middle-aged subjects and blood-borne metastasis is common), anaplastic (15%; affects elderly and is rapidly invasive) and medullary carcinoma (5%; associated with MEN 2 syndrome). Predisposing factors include prior irradiation of the neck and a positive family history.

➢ Patients are usually euthyroid and often present with a nodular thyroid enlargement.

➢ Investigations include RAIU (to assess nodule function), and FNAC for cytologic diagnosis. Calcitonin levels are increased in medullary cancer.

➢ Thyroid cancers are treated with total thyroidectomy followed by radioiodine ablation (except for medullary cancer) and hormone replacement. Relatives of patients with medullary cancer are screened for MEN syndrome.

16.6 Diseases of the parathyroid glands and metabolic bone disease

Parathyroid Glands

The parathyroid glands comprise four small glands located on the posterior aspect of the thyroid gland. Sometimes they may be embedded in the thyroid tissue. The glands may vary in their position, the lower pair more often than the upper pair. The average total weight of the four glands is 120 mg, but the individual normal gland can weigh as much as 70 mg.

The main function of these glands is to secrete *parathormone* (PTH), which is the hormone regulating calcium homeostasis. PTH acts to increase renal reabsorption of calcium and magnesium, and increases renal phosphate excretion. PTH also stimulates 25, (OH)D 1α hydroxylase in the kidney to increase hydroxylation of 25-hydroxyvitamin D to 1,25 dihydroxyvitamin D. The latter is the active form of vitamin D and increases calcium absorption from the intestine. PTH also acts on bone (which is the main reservoir of calcium in the body), to increase bone resorption and mobilise calcium. To a lesser extent, bone formation is also stimulated by PTH. By all the above actions PTH increases plasma calcium and lowers phosphate concentrations.

PRIMARY HYPERPARATHYROIDISM

Etiopathogenesis This is a disorder caused by the excessive secretion of parathyroid hormone by one or more of the parathyroid glands. Since parathyroid hormone (PTH) causes mobilisation of calcium from the bone and reduces renal excretion of calcium, this disorder is characterised by hypercalcemia. *Primary hyperparathyroidism* is one of the two most common conditions associated with hypercalcemia, the other being malignancy-associated hypercalcemia.

The prevalence of primary hyperparathyroidism ranges from 1 in 500 to 1 in 1000 of the general population. In the countries where routine use of the autoanalyser (which measures calcium levels as a part of a panel of tests) is common, the incidence of the disease has been increasing and most patients are discovered incidentally based on a blood test which was ordered for some other reason. Older women in the sixth decade of life are more commonly affected.

Most (about 80 per cent) of patients with primary hyperparathyroidism have an abnormality of a single parathyroid gland. The gland is enlarged and secretes PTH in an uncontrolled manner not subject to the normal feedback by the increased serum calcium levels. This condition is called a *parathyroid adenoma.* The other three parathyroid glands are shrunken as they are inhibited by the high levels of calcium. The adenomatous gland is surrounded by a capsule and weighs much more (usually over 200 mg) than the usual weight of a normal gland (which is about 25 mg). The gross appearance and weight of the gland are the main clues to the fact that the gland is adenomatous. Microscopically, the gland has cells appearing normal though there may be less fatty tissue than seen in normal glands.

About 20 per cent of patients have a pathologic process involving all four glands which are uniformly enlarged; this is called *parathyroid hyperplasia.* Patients with parathyroid hyperplasia may have a familial tendency where they may also get other endocrine tumours. Such a condition is called the *multiple endocrine neoplasia syndrome* (MEN). MEN syndromes are classifed as *MEN 1* where pituitary adenomas, and pancreatic tumours (such as insulinoma and glucagonoma) occur in association with parathyroid hyperplasia. *MEN 2* is the association of parathyroid hyperplasia with medullary carcinoma of the thyroid and adrenal pheochromocytoma. Some patients of MEN 2 have soft tissue tumours of the oral mucosa (*mucosal neuromas*) and are further subclassified as *MEN 2-b.*

The distinction between parathyroid adenoma and hyperplasia is an important one for the treatment of a patient. In the former, the removal of the single pathologic gland is curative, whereas in the latter, almost all the parathyroid tissue may have to be removed to achieve normocalcemia.

A rare cause of primary hyperparathyroidism is *parathyroid carcinoma.* The presence of vascular invasion and metastases help to make this diagnosis.

Clinical manifestations The clinical manifestations of hyperparathyroidism can be divided into two major groups: those directly due to hypercalcemia, and those as a consequence of the actions of PTH on tissues, mainly the bone and the kidney. The enlargement of the parathyroid tissue is rarely appreciated on clinical examination. If a parathyroid mass is palpated, parathyroid carcinoma should be excluded.

Hypercalcemia presents with the symptoms of polyuria, polydipsia, anorexia, constipation, and depressed central nervous function. Often the symptoms of hypercalcemia are so non-specific, that they may be ignored. A clue to the presence of hypercalcemia is a shortened QT interval on an electrocardiogram. In rare cases, calcium phosphate deposits are seen on the medial and lateral limbic margins of the cornea (*band keratopathy*) on slit lamp examination.

High levels of PTH lead to certain bone changes, some of which are typical for this disorder. Resorption of the bone leads to typical radiologic signs of subperiosteal resorption of the distal phalanges, and a moth-eaten or *'salt and pepper'* pattern in the skull. Locally destructive lesions (which are collections of osteoclasts) are seen in the long bones and called *brown tumours.* Generalised demineralisation of the bone leads to an increased propensity for fractures, and bone pain. Before radiological signs are evident, a reduction in bone density may be seen with more sophisticated methods of non-invasive densitometry. *Dual energy X-ray absorptiometry* (DEXA) is commonly employed since it reliably measures bone mineral density with very low doses of radiation. Measurement of bone mineral density shows a greater effect of elevated PTH on the cortical bone (as seen in the radius) than on the cancellous bone (as seen in the lumbar spine).

Patients with hyperparathyroidism often have high urinary calcium excretion rates. This is despite the fact that PTH acts to increase urinary reabsorption of calcium. The *hypercalciuria* occurs because the greater load of filtered calcium due to hypercalcemia exceeds the reabsorptive capacity of the kidneys. Besides hypercalciuria, renal stones and *nephrocalcinosis* (deposition of calcium phosphate deposits throughout the renal parenchyma) occur more frequently with hyperparathyroidism. Fortunately, with earlier diagnosis these complications are seen less frequently.

Other complications of this condition include *pseudogout,* a normochromic, normocytic anemia, and increased fatiguability.

Diagnosis Patients with primary hyperparathyroidism exhibit a wide range of serum calcium

levels, ranging from only mildly elevated levels to very high levels. The serum phosphorus levels may be in the low normal range or frankly low. This is due to the *phosphate-wasting effect* of PTH on the renal tubules. The bone-derived fraction of serum alkaline phosphatase is elevated as is serum *osteocalcin,* both of which are measures of osteoblastic activity. *Urinary hydroxyproline* level are raised and reflect increased osteoclastic activity. Since PTH increases renal conversion of 25 OH vitamin D to 1,25 $(OH)_2D$, levels of 1,25 dihydroxyvitamin D may also be elevated. However, this finding is not specific for hyperparathyroidism, as elevated levels of 1,25 dihydroxyvitamin D may be seen is association with hypercalcemia in sarcoidosis and vitamin D toxicity.

In about 25 per cent of the patients, urinary calcium levels may be elevated. Urinary phosphorus excretion is high in most patients. Since PTH acts to generate cAMP in the kidney, *urinary cAMP* is increased in primary hyperparathyroidism.

The most useful test for the diagnosis of primary hyperparathyroidism is the measurement of the parathyroid hormone level. The most useful assays are those which measure the intact hormone, that is, the entire molecule. Assays which measure only the N terminal or C terminal of the peptide may measure related peptides or degradation products and are less specific. The combination of high PTH in association with hypercalcemia is highly suggestive of primary hyperparathyroidism, with the only exceptions being hypercalcemia secondary to thiazide diuretics or lithium. In all other cases of hypercalcemia (such as malignancy and vitamin D excess) the PTH levels are suppressed. In humoral hypercalcemia of malignancy, another peptide called the *PTH-related peptide* (PTH-rP) is elevated, and the assay for PTH does not cross-react with the assay for the PTH-rP.

In patients with hypercalcemia and suppressed PTH levels in whom another cause for hypercalcemia is not evident *familial hypocalciuric hypercalcemia (FHH)* should be considered. These patients have very low urinary calcium excretion and are free from the complications of primary hyperparathyroidism, and hence need no treatment.

Treatment The definitive treatment for primary hyperparathyroidism which is accompanied by signs and symptoms is surgical removal of the abnormal gland(s). In the completely asymptomatic patient with mild hypercalcemia (picked up on routine laboratory work-up) the role of surgery is uncertain, since it is difficult to predict who will ultimately develop the complications of parathyroid disease. It seems that many patients remain well for years despite minor elevations in serum calcium and PTH.

Current guidelines for surgery include: 1) serum calcium level greater than 1 mg/dL above the upper limits of normal; 2) signs or symptoms of primary hyperparathyroidism regardless of calcium values; 3) markedly reduced cortical bone density; 4) an episode of acute primary hyperparathyroidism, that is, acute hypercalcemia leading to dehydration and other symptoms; 6) hypercalciuria or renal stone disease; and 7) young age at presentation, as it is assumed that a long duration of high PTH levels are more likely to eventually cause problems.

The surgery should be performed by a surgeon who is familiar with the procedure since the parathyroids are small and are sometimes located in ectopic locations. When an adenoma is discovered the abnormal parathyroid alone is removed. If parathyroid hyperplasia is seen, the usual procedure is to remove three-and-a-half glands. The remaining half gland is either left in place or transplanted into the forearm, so that a repeat neck exploration could be avoided should reoperation ever be necessary. The major complication of the surgery is usually transient hypocalcemia, which corrects itself in a few days. Sometimes hypocalcemia is more prolonged as a

result of deposition of calcium into the bone following the removal of the high PTH effect on the bone (*hungry bone syndrome*). Rarely, there may be permanent hypoparathyroidism or recurrent laryngeal nerve palsy following parathyroidectomy.

There are a number of tests used to identify the abnormal parathyroid gland(s) preoperatively. However, they are not very reliable and most surgeons feel that the best approach is to visualise all the glands during surgery as the appearance of the glands is the best indicator. The pathology of the gland can be checked during the surgery by frozen sections of the tissue to guide the surgeon further.

In patients in whom the surgical option is not chosen, adequate hydration and ambulation should be ensured. Drugs which cause hypercalcemia (such as lithium and thiazides) should be avoided. Vitamin D levels and the daily intake of calcium should be kept in the normal range. Oral phosphate therapy may be used to prevent hypophosphatemia and to enhance calcium phosphate deposition in bone, though it may also predispose to ectopic calcium phosphate deposition. In postmenopausal women, estrogen therapy may act to increase bone mineralisation and reduce urine calcium excretion. Trials are underway to determine whether a class of drugs known as the biphosphonates, which inhibit osteoclastic activity, have a role in preventing the complications of hyperparathyroidism. All patients of primary hyperparathyroidism should be followed up for the development of complications.

HYPOPARATHYROIDISM

Etiopathogenesis Hypoparathyroidism occurs either due to decreased PTH secretion or resistance to actions of PTH secondary to receptor abnormalities. Absence of the effect of PTH on bone and the kidneys leads to hypocalcemia and hyperphosphatemia, which are the main manifestations of this condition.

The causes of hypoparathyroidism are :

1. Deficiency in PTH secretion
   a. Surgical — post neck surgery
   b. Idiopathic hypoparathyroidism, sometimes familial
   c. Hypomagnesemia (inhibits PTH release)
   d. Metastases to parathyroid
   e. Iron storage disorders: thalassemia associated hemosiderosis; hemochromatosis
   f. Di George syndrome – parathyroid and thymic aplasia with cardiac malformations
   g. Post radioiodine treatment of thyroid disease (rare)
2. Resistance to PTH effect
   Pseudohypoparathyroidism — normal PTH levels, characteristic skeletal abnormalities, metabolic abnormalities of hypoparathyroidism.

[Note: *Pseudopseudohypoparathyroidism* is a term used for individuals with the typical skeletal abnormalities of pseudohypoparathyroidism but no hypocalcemia or demonstrable metabolic defects].

Clinical features The clinical manifestations of hypoparathyroidism occur either secondary to the hypocalcemia and hyperphosphatemia or are linked specifically to the cause of the disorder (Fig 16.17).

Decreased plasma calcium levels lead to mild paresthesiae which manifests as perioral numbness and tingling of hands and feet, and increased neuromuscular irritability which may be elicited by the *Chvostek* or *Trousseau signs*. At a later stage there may be cramps, carpopedal spasm, stridor and convulsions. There may be mental changes of irritability, depression or even frank psychosis. Chronic hypocalcemia may be associated with papilledema and elevated cerebrospinal fluid pressure.

Hypocalcemia is associated with prolongation of the QT interval on the ECG, though this rarely causes arrhythmias. Prolonged hypocalcemia leads to ectopic calcification of the basal ganglia and the lens in the eye. Depending on the age of onset of hypocalcemia, there is hypoplasia of dentition.

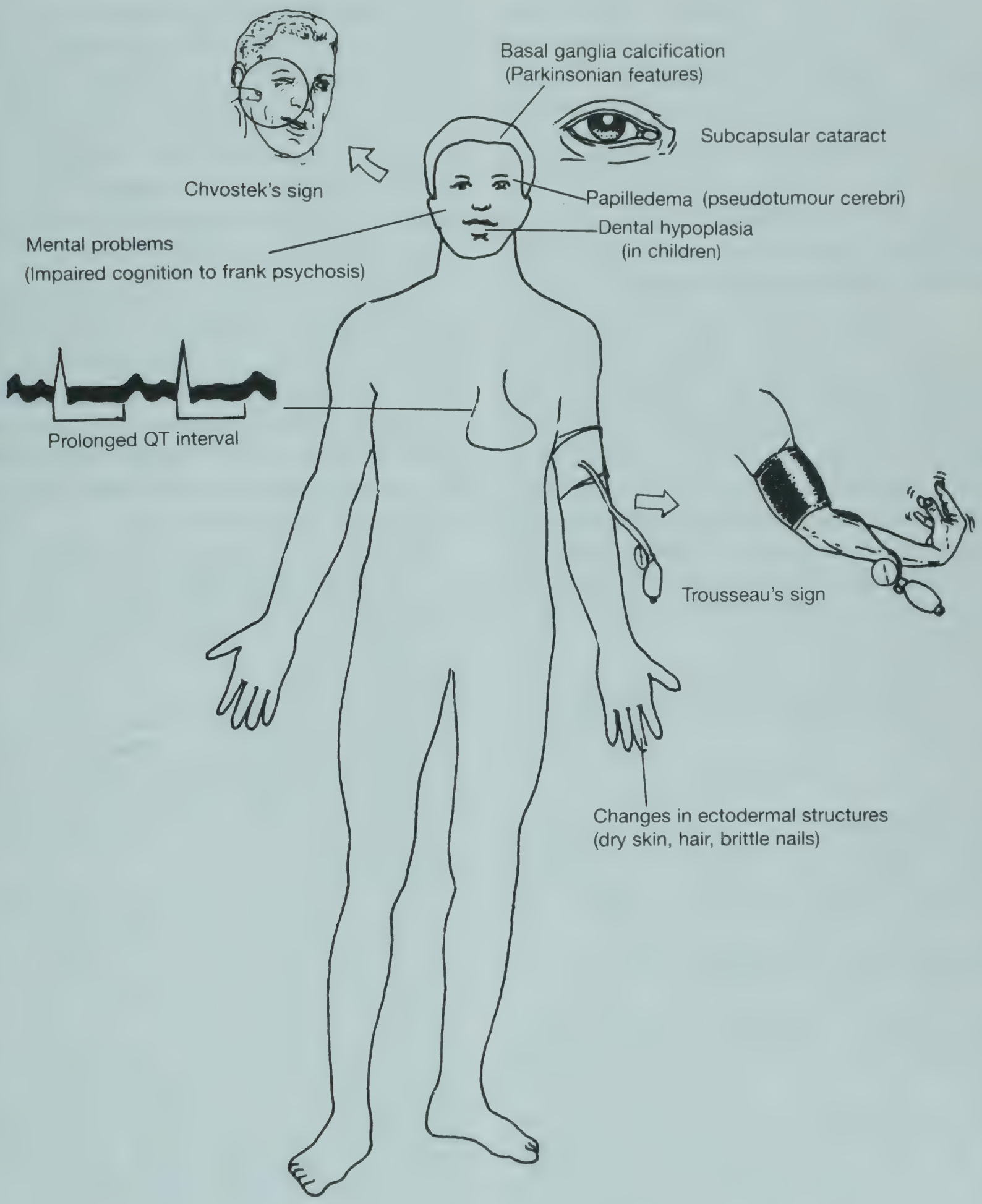


Fig 16.17 Clinical features of hypoparathyroidism

There may be clues on the clinical examination to the underlying cause of the hypoparathyroidism. Vitiligo and other autoimmune diseases are associated with idiopathic hypoparathyroidism. These patients are also more prone to oral candidiasis. The presence of a neck scar or a history of surgery would suggest surgical hypoparathyroidism. Patients with pseudohypoparathyroidism have the typical skeletal features of short stature and short fourth metacarpals. They are also obese and tend to have reduced intelligence.

Treatment The therapy of hypoparathyroidism is Vitamin D and calcium supplements regardless of the cause. Vitamin D is used in the dose of 50,000–100,000 IU/day, with 1–2 g of elemental calcium/day. The dose has to be individualised to maintain normal calcium levels. Magnesium should be replaced if serum levels are low. Phosphorus need not be replaced since renal clearance of phosphate increases with correction of hypocalcemia, which lowers phosphorus concentration.

METABOLIC BONE DISEASE

Osteoporosis

Osteoporosis may be defined as a disorder characterised by a low bone mass in association with a tendency towards bone fractures even from minor trauma. Osteoporosis affects a third to one half of postmenopausal women and one half of all people over the age of 75 years.

Pathogenesis The human skeletal system is composed of *cortical* (80%) and *trabecular* (20%) bone. Bone continually undergoes *remodelling* during adult life; about 10 per cent of the adult skeleton undergoes remodelling every year. Remodelling consists of bone resorption along with new bone formation. Remodelling begins with increased activity of the osteoclasts. These bone-resorbing cells create a cavity within cortical bone or a *lacuna* on the surface of the trabecular (also called cancellous) bone. The osteoclasts are then replaced by osteoblasts which gradually refill the spaces created by osteoclastic activity. Osteoporosis is characterised by a net loss of bone due to remodelling. This may arise from excessive osteoclastic activity (creating cavities or lacunae which are too deep), or due to a failure of the osteoblasts to refill a resorption cavity, or due to a combination of the two processes.

The osteoporotic bone lacks the strength of the normal bone. Fractures may result with relatively minor trauma. Since trabecular bone is more metabolically active, osteoporotic fractures are more common at sites composed of greater than 50 per cent trabecular bone. Typical sites include the vertebral body, the distal forearm and the proximal femur.

Risk factors for osteoporosis include female sex, advanced age, premature or early menopause, prolonged immobilisation, excess alcohol consumption, a thin body habitus and smoking.

Types of osteoporosis

Type I osteoporosis (also called *postmenopausal* osteoporosis) results from accelerated bone loss in the postmenopausal period due to estrogen deficiency. This affects women in the sixth and seventh decade who sustain vertebral or forearm bone fractures.

Type II osteoporosis (also called *senile* osteoporosis) is the result of a slower age-related loss of bone in both sexes. The typical manifestation is a fracture of the proximal femur in elderly subjects (>75 years).

Secondary osteoporosis accounts for about 20–40 per cent of cases. It is related to endocrine (hypercortisol state, hyperparathyroidism, hyperthyroidism), gastrointestinal disease (malabsorption syndrome, liver disease such as primary biliary cirrhosis), immunoinflammatory diseases (rheumatoid arthritis, seronegative spondyloarthropathies) or drugs (notably prolonged use of corticosteroids or heparin).

Clinical features and investigations Osteoporosis is often an incidental finding when the spine is being examined for another illness. Manifestations include a tendency to fractures after minor trauma, a loss of height, or spontaneous vertebral fractures, which are often asymptomatic.

Typically, the serum calcium, phosphorus and alkaline phosphatase are in the normal range. Osteoporosis can be detected with X-rays of the involved bones, usually the spine and pelvis. However, *osteopenia* (bone loss) cannot be reliably diagnosed by plain X-rays and bone densitometry is required for this purpose. Bone densitometry[1] permits early detection of the preclinical stages of demineralisation. Bone density is a good predictor of a person's risk of a fracture. The lumbar spine and proximal femur are the common sites for assessment of bone density.

Treatment The treatment of osteoporosis depends on its cause. If reversible causes (such as drug use) are present, they should be reversed. Dietary calcium supplementation (1500 mg/day) and a moderate exercise routine are recommended. Physiological doses of vitamin D may be used as adjunctive therapy. Estrogens (0.625 mg/day of conjugated estrogen or 1 mg/day of estradiol administered orally or as a patch) seem to decrease the rate of bone resorption and have been used prophylactically in individuals whose bone mineral density is one standard deviation below that predicted for the particular age. Osteoporotic subjects with severe bone pains may be treated with calcitonin (salmon calcitonin, 100 IU subcutaneous or i.m. every other day). Thiazide diuretics may be helpful if there is associated hypercalciuria. Alcohol should be avoided. Diphosphonate compounds also inhibit bone resorption; etidronate (400 mg daily for 2 weeks, every 3 months) may also be used to treat osteoporosis. If severe pain is present, analgesics may be required. Since falls usually precipitate fractures in osteoporotic subjects, fall prevention strategies are important. These include avoiding postural hypotension, avoiding sedative medications and removing environmental hazards such as loose floor mats, protruding wires and cables, and wet floors.

[1] Techniques include *dual-photon absorptiometry (DPA)* and *dual-energy X-ray absorptiometry (DEXA)*

Osteomalacia

Osteomalacia[2] is a condition seen in adults which results from defective mineralisation of osteoid formed during bone remodelling.

Pathophysiology As discussed in the previous section, normal adult bone undergoes continuous remodelling. During remodelling, the osteoblasts lay down newly formed bone called *osteoid.* The osteoid then undergoes mineralisation with the deposition of bone salts. The mineralisation of osteoid requires a normal *ion product* of calcium and phosphorus and normal function and levels of vitamin D. In osteomalacia, the mineralisation of osteoid is defective. Consequently, the osteoid seams are wider and the remodelled bone is weaker. The widened seams become visible by X-ray and the cortex of bones shows incomplete ribbon-like areas of demineralisation (*Looser's zones* or *pseudofractures*). The soft weight-bearing bones bend resulting in bowing of long bones, vertical shortening of vertebrae, and flattening of the pelvic bones thus contracting the pelvic outlet.

Etiology Osteomalacia results from inadequate bioavailability of the active form of vitamin D, chronic phosphate depletion, or the presence of inhibitors of mineralisation. The causes are listed in Table 16.17.

Clinical features The clinical features of osteomalacia are often subtle initially. An aching pain in the bones and tenderness of bones may be seen. As osteomalacia becomes more severe,

[2] Osteomalacia means bone softening

Table 16.17 Causes of osteomalacia

A. Vitamin D deficiency
   1. Decreased availability of vitamin D (dietary lack, malabsorption syndrome, high phytate diet, lack of sunlight)
   2. Defects related to production of 25-(OH) vitamin D_3
      - liver diseases
      - drugs (anticonvulsants)
   3. Defects related to action of 1,25 $(OH)_2$ vitamin D_3
      - renal failure
      - Vitamin D-dependent rickets

B. Phosphate deficiency
   1. Decreased intestinal absorption (malabsorption syndrome, antacids)
   2. Increased renal loss (chronic renal failure, renal tubular disorders)

C. Inhibitors of mineralisation (aluminium, diphosphonates)

D. Hereditary hypophosphatasia

a weakness of proximal and pelvic girdle muscles may be seen. This accounts for the typical *waddling gait* in some of these patients. *Narrowing of the pelvic outlet* may be associated with difficulties at the time of childbirth in a pregnant woman with osteomalacia.

Investigations The laboratory features depend on the underlying etiology. If renal failure is absent, the usual findings are those of mild hypocalcemia, moderate hypophosphatemia, and elevated alkaline phosphatase levels. If alkaline phosphate levels are normal, the rare disorder *hypophosphatasia* may be present. In this rare autosomal recessive disorder adults generally have only mild osteomalacia; elevated urinary levels of phosphorylethanolamine and pyrophosphate are associated findings.

The X-ray findings usually corroborate the clinical diagnosis; *pseudofractures* are typically seen on the pubic and ischial rami, neck of the femur, the ribs and the axillary margins o the scapulae.

Treatment Treatment of osteomalacia depends on the underlying etiology. Nutritiona deficiency of vitamin D can be correcte with oral vitamin D (1600 IU/day, taperec after 1 month). Larger doses are required i malabsorption syndromes. Vitamin D resistanc syndrome responds to replacement of 25-OH vitamin D (calcifediol) or 1,25-$(OH)_2$ vitamin D (calcitriol). Phosphate deficiency due to rena phosphate wasting responds to phosphat supplementation. Treatment of rena osteodystrophy has been discussed in the sectio on renal disorders.

Paget's Disease of the Bone (Osteitis Deformans)

This is a rare disorder characterised by chroni localised areas of bone destruction which ar replaced by softened and exuberant areas o osseous repair. It is thought that the disorde may be related to a paramyxovirus (*canin distemper virus*). The disorder is seen in middle aged subjects who experience pain in the area o bone involved. The sacrum, skull, pelvis an spine are frequently involved. Bon enlargements are typical: a hat or cap which n longer fits, a hobbling gait or anterolater bowing deformity of the tibia. Involvement o the spine can result in spinal cord compressio and skull involvement can result in deafness. high cardiac output state is usually present as th areas of osseous repair are very vascular. Th skin over the involved bones may feel warm an the optic fundi may show *angioid streaks*. On per cent of affected patients can develop sarcomatous change in the involved bone.

The X-ray picture is typical with expande and dense bones which are bowed and may hav microfractures. Alkaline phosphatase levels a very high while serum calcium and phosphor levels are normal. **Treatment** consists phosphonates (etidronate) and calcitonin.

KEY CONCEPTS

Hyperparathyroidism

- Autonomous production of PTH may be due to a parathyroid adenoma (80%), hyperplasia (~20%), or rarely, a carcinoma. The condition may be part of MEN 1 or 2.
- In Europe and North America, hyperparathyroidism is most often discovered due to hypercalcemia noted incidentally on serum chemistry results obtained for some other purpose. Hypercalcemia results in anorexia, nausea, constipation, renal calculus disease, dyspepsia, bone pain and emotional changes (or altered mentation).
- Serum levels of ionised calcium are elevated while serum phosphate is low. ALP is elevated in proportion to the degree of bone disease.
- X-ray appearance may be diagnostic; osteopenia, subperiosteal erosion of phalanges, erosion of lamina dura of teeth, brown tumours, and a pepper pot skull are some features.
- An ultrasound of the neck, a radionuclide scan of the parathyroid, and CT/MRI scans are methods for detecting parathyroid adenomas.
- Treatment includes surgical excision of an adenoma; for parathyroid hyperplasia removal of three of the four glands with reimplantation of the fourth in the forearm is recommended. General measures to combat hypercalcemia include rehydration with saline and the use of biphosphonates.

Hypoparathyroidism

- Hypoparathyroidism (low levels of PTH) may be autoimmune in origin (primary), or may occur post-thyroid surgery (secondary).
- Pseudohypoparathyroidism is a condition with resistance to the action of PTH (resulting in hypoparathyroidism) with additional skeletal abnormalities (short stature, short fourth metacarpal) and mental retardation. Pseudopseudo-hypoparathyrodism is a condition with similar phenotypic features but the serum biochemistry is normal.
- The clinical features of hypoparathyroidism may be due to acute or chronic hypocalcemia. Acute hypocalcemia results in neuromuscular irritability: tetany, perioral paresthesia, cramps and positive Trousseau or Chvostek signs. Chronic hypocalcemia results in brittle ridged nails, hypoplastic teeth with enamel defects and dry, scaly skin. There may be associated mucocutaneous candidiasis.
- Laboratory investigations reveal hypocalcemia, increased serum phosphate levels, and normal alkaline phosphatase levels. Calcification of the basal ganglia may be noted. Reduced plasma PTH levels are diagnostic. An increase in urinary cAMP on infusion of PTH confirms normal end organ response in hypoparathyroidism (failure of response indicates pseudohypoparathyroidism).
- Acute hypocalcemia can be treated with intravenous calcium gluconate initially. Administration of alpha-vitamin D_3 (0.25–2 μg/d) and calcium supplementation are long term measures.

Multiple endocrine neoplasia (MEN) syndromes

- This is group of familial disorders characterised by multiple neoplasms affecting the endocrine system. The disorders may be autosomal dominant with variable penetrance or familial.
- Possible tumours occurring alone or in combination in the MEN syndromes are listed. MEN type 1 (*Wermer syndrome*): pituitary adenoma, parathyroid adenoma, and pancreatic islet cell tumour. MEN type 2a (*Sipple syndrome*): parathyroid adenoma, medullary carcinoma thyroid, pheochromocytoma. MEN type 2b: medullary carcinoma thyroid in association with mucosal neuromas and a Marfanoid habitus.
- Treatment consists of surgical excision of the underlying tumours. First-degree relatives must be screened for the conditon to detect asymptomatic neoplasms at an early stage.

Osteoporosis

- Osteoporosis is characterised by a reduction in bone mass. The characteristic histologic feature is loss of bone matrix and minerals, while the clinical manifestation is a propensity for skeletal fractures.
- Osteoporosis may be *senile* (aging-related; fractures of cortical [e.g., hip] and trabecular [e.g., vertebra] bones) or *postmenopausal* (women; trabecular bones involved). Factors contributing to the development of osteoporosis include corticosteroid therapy, or smoking, thin build and lack of exercise.
- Clinical features include bone pain, backache, and fractures (hip and vertebral fractures, Colles' fracture).
- Serum chemistry (calcium, phosphate, alkaline phosphatase) is normal. X-ray of the spine reveals a decreased bone density, vertebral fractures and wedge-shaped deformities. Dual photon densitometry or DEXA are investigations for assessing bone mass.
- Treatment consists of regular exercise, calcium, and vitamin D supplements, estrogen use in women, biphosphonates and calcitonin use.

Osteomalacia

- Osteomalacia results from an incomplete mineralisation of the osteoid (newly formed bone matrix). Causes include vitamin D deficiency, malabsorption, or vitamin D resistance.
- Such deficiency results in rickets in the growing child and in osteomalacia in adults. Clinical features in adults include bone pains and a proximal myopathy.
- Laboratory investigations include hypocalcemia, hypophosphatemia and elevated alkaline phosphatase levels. Definitive diagnosis requires a bone biopsy but may not usually be necessary. Radiologic findings include *pseudofractures* (Looser's zones) most evident on the pubic rami, scapula and the femur.
- Treatment includes calcium supplementation and administration of calcitriol.

Paget's disease of the bone

- This disease is characterised by increased osteoclastic bone resorption which is followed by disorderly osteoblastic activity. The new bone is structurally weak. There is a small risk of sarcomatous degeneration.
- Clinical features are related to bony enlargement and increased cardiac output (due to increased vascularity of newly formed bone). Deafness is common as are symptoms due to nerve compression.
- Laboratory investigations are normal except for elevated alkaline phosphatase levels and increased urinary hydroxyproline. Skeletal X-rays (pelvis, femur) show evidence of osteolysis and osteosclerosis.
- Asymptomatic patients do not require any treatment. In symptomatic patients, therapeutic options include calcitonin (for inhibiting osteoclastic activity), diphosphonates and analgesics (for pain).

16.7 Diseases of the adrenal gland

The Adrenal Gland

The adrenal glands are paired organs located in relation to the upper pole of the kidneys. Each gland is composed of an outer *cortex* and inner *medulla,* both of which are of different embryological origin and have distinct functions. The cortex is responsible for the synthesis of cortisol, aldosterone and adrenal androgens, while the cells in the medulla synthesise cathecholamines. Each gland weighs 3–5 grams normally, but enlarges in response to stress, when there is increased cortisol production.

The cells forming the cortex can be divided into three zones: an outer *zona glomerulosa,* the middle *zona fasciculata,* and the inner *zona reticularis.* Physiologically, these zones have distinct functions: the glomerulosa secretes aldosterone, while the fasciculata and reticularis synthesise cortisol and adrenal androgens. The medulla is made up of *chromaffin* cells which are of neural crest origin and are the equivalent of postganglionic sympathetic neuronal cells.

Physiology The adrenal cortex synthesises compounds which have the steroid nucleus as their basic structure consisting of three 6-carbon hexane rings and a single 5-carbon pentane ring (Fig 16.18). Adrenal steroids which include aldosterone, cortisol and androgens, share this common structure.

Adrenal steroids have either 19 or 21 carbon atoms. The C_{19} steroids have methyl groups at position C_{18} and C_{19}. The C_{21} steroids are otherwise similar in structure to $C_{19,}$ but in addition have a 2-carbon side-chain (C_{-20}, C_{-21}) at position 17. The C_{19} steroids have predominantly androgenic activity whereas the C_{21} steroids have either glucocorticoid (cortisol-like) or mineralocorticoid (aldosterone-like) activity.

The starting compound for steroid synthesis is cholesterol. The adrenal cells have LDL receptors to bind cholesterol from the circulation, but also have the capability to synthesise their own cholesterol. Depending on

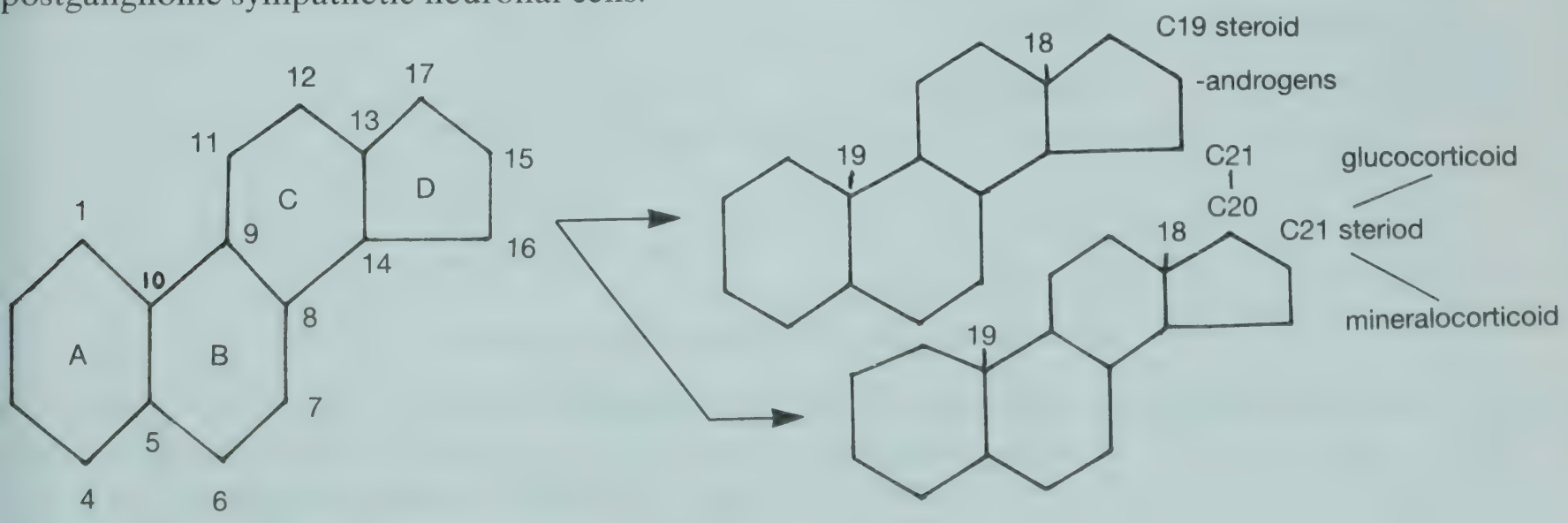


Fig 16.18 Structure of adrenal steroids

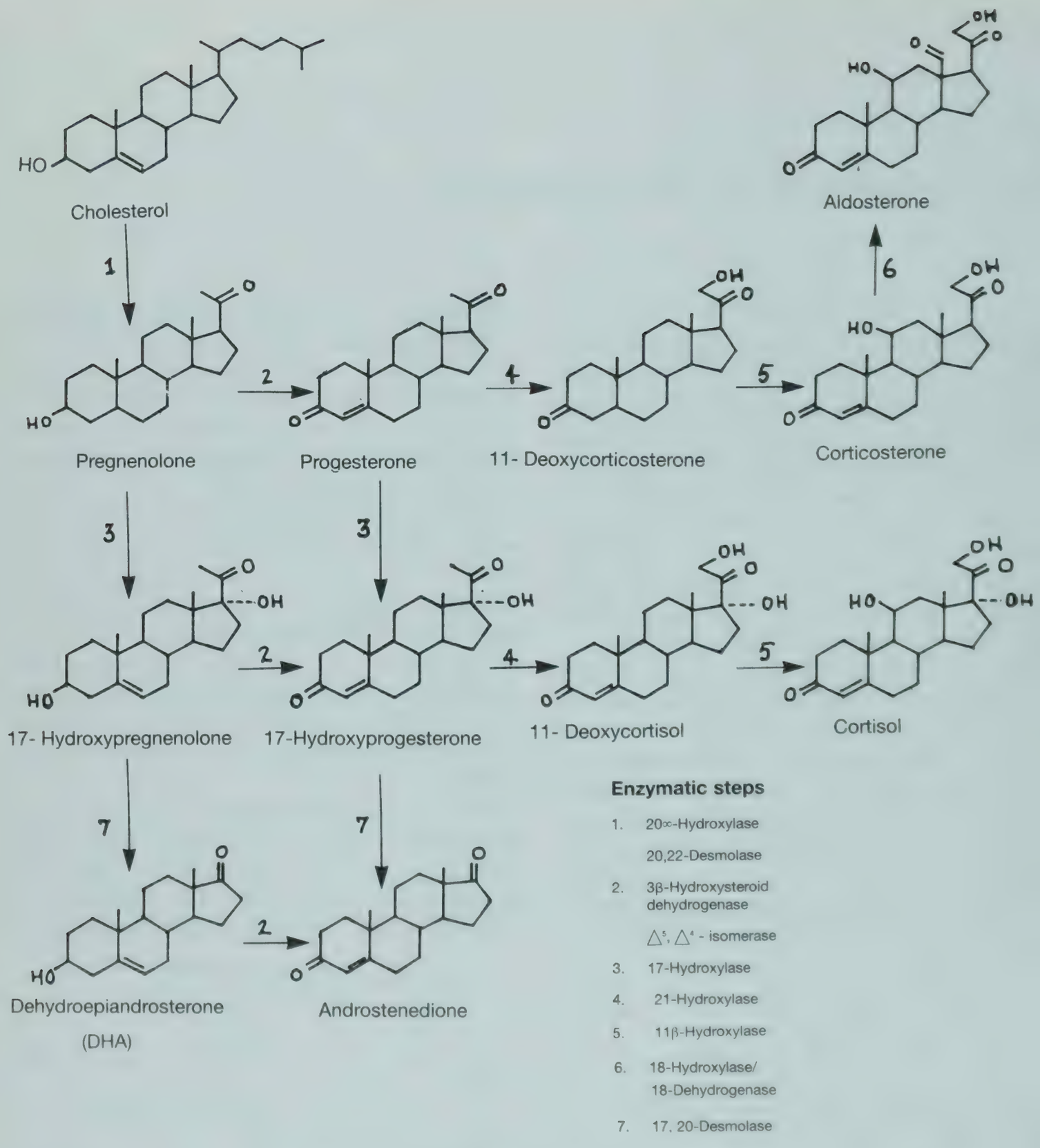


Fig 16.19 Biosynthetic pathways for adrenal steroids

the enzymatic capacity of each zone of the cortex, different steps in the biosynthetic pathway occur, leading to a predominance of particular steroids being made in different zones. The pathways for the synthesis of the different adrenal steroids is shown i Fig 16.19. As can be seen from this figure, th major mineralocorticoid is *aldosterone* and th major glucocorticoid is *cortisol*. The majo androgens synthesised in the adrenals ar

dehydroepiandrosterone (DHEA), and androstenedione. DHEA is subsequently sulphated to DHEA sulphate. The androstenedione is converted to testosterone in the peripheral tissues by *17-ketosteroid reductase,* or to estrogens by the *aromatase* enzyme in adipose tissue. About 50 per cent of circulating androgens in females, and only 2 per cent of androgens in the male are of adrenal origin. The rest of the androgens come from the gonads in both sexes. The androgens from the adrenals (DHEA and androstenedione) have weak androgenic activity compared to testosterone.

Physiologically, the most relevant hormones synthesised by the adrenal are the glucocorticoids and the mineralocorticoids. The most potent mineralocorticoid is aldosterone, though cortisol has mild mineralocorticoid activity too. Mineralocorticoid activity is defined as the ability of a substance to affect the metabolism of sodium and water. Mineralocorticoids cause the retention of sodium and the elimination of potassium and hydrogen ion. Aldosterone has its predominant action on the collecting tubules in the kidney. It acts on the cortical portion of the collecting tubule to retain sodium in exchange for potassium, and on the medullary portion to retain sodium in exchange for the hydrogen ion. Sodium retention causes retention of water, and this leads to a tendency for volume overload and hypertension. Due to poorly understood mechanisms, the amount of sodium and water retention caused by unopposed mineralocorticoid action is limited in healthy individuals. After a certain degree of sodium and water retention, there is an *escape* from the effect of aldosterone on the kidneys. However, in patients who have high aldosterone levels secondary to low sodium delivery to renal tubules, leading to stimulation of renin and angiotensin (*secondary hyperaldosteronism*), the sodium and fluid retention is more impressive. This state occurs in conditions such as congestive cardiac failure, nephrotic syndrome, and liver disease.

The secretion of aldosterone from the zona granulosa cells is dependent on two factors:

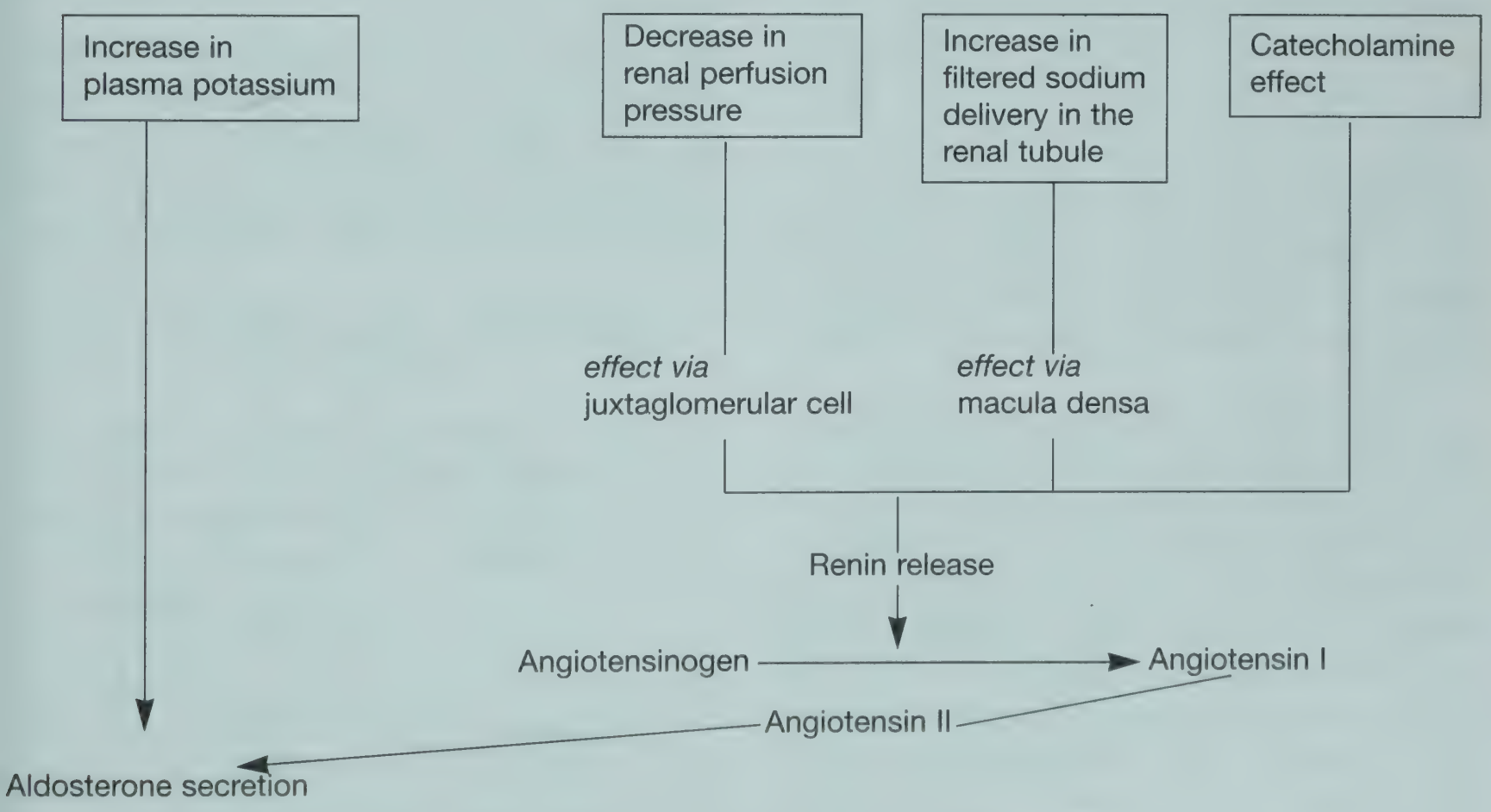


Fig 16.20 Control of aldosterone secretion

1) the stimulation by angiotensin II, the production of which is in turn dependent on renin (the renin-angiotensin system), and 2) the plasma potassium level. The details of aldosterone stimulation are shown in Fig 16.20.

Glucocorticoids act at many steps in the intermediary metabolism and their actions are somewhat complex. They act on carbohydrate metabolism to increase hepatic glucose production by *increase in gluconeogenesis*. They also reduce tissue glucose uptake, by inducing a resistance to the action of insulin. By these mechanisms cortisol causes a tendency to *hyperglycemia,* and opposes the actions of insulin. However, cortisol acts in parallel with insulin to *increase glycogen synthesis* in the liver and to restrict glycogen breakdown.

In concert with epinephrine and glucagon, cortisol causes an *increase in lipolysis* and increased free fatty acid levels. The action on adipose tissue is differential causing depletion of peripheral fat with increased fat deposition in the abdominal region. Cortisol also causes *proteolysis* in skeletal muscle, thereby releasing amino acid substrate for gluconeogenesis.

Glucocorticoids inhibit most inflammatory and immunologic responses. They cause lymphopenia but increase the release of polymorphonuclear cells from the bone marrow. Although the neutrophil numbers are increased, their function is depressed. Absolute eosinophil numbers are reduced by cortisol, and for this reason eosinophilia is seen with cortisol deficiency.

Cortisol inhibits skin fibroblasts and this leads to the thin skin and easy bruising associated with cortisol excess. Cortisol tends to reduce intestinal calcium absorption and renal calcium reabsorption which in turn stimulates PTH secretion. It also stimulates osteoclastic activity, and this along with the higher levels of PTH lead to increased osteolysis. For this reason, excess glucocorticoids are associated with osteoporosis. Another action of cortisol on bone is the inhibition of growth at the epiphyses, which is the main concern when its use is considered in children.

Glucocorticoids also act on the central nervous system to influence mood and behaviour. Small amounts of excess lead to euphoria—an effect sometimes observed in patients receiving a small dose for therapeutic purposes. Higher levels may lead to psychosis. Deficiency of cortisol manifests as irritability and memory loss. Depression may be associated with states of both deficiency and excess.

Secretion of glucocorticoids from the zona fasciculata and reticularis is under control of corticotropin (ACTH), a peptide hormone synthesised by the anterior pituitary. The major factors controlling ACTH release are 1) corticotropin releasing hormone (CRH) from the paraventricular nucleus in the hypothalamus 2) free cortisol levels in the plasma (negative feedback); and 3) a set diurnal pattern. Stressful events also cause an increase in ACTH release (Fig 16.21)

Laboratory assessment of adrenocortical function

Blood levels: ACTH and angiotensin II can be measured in the blood by radioimmunoassay. Both fluctuate during the day. In addition a circadian rhythm occurs in ACTH levels, while angiotensin II levels change with sodium intake

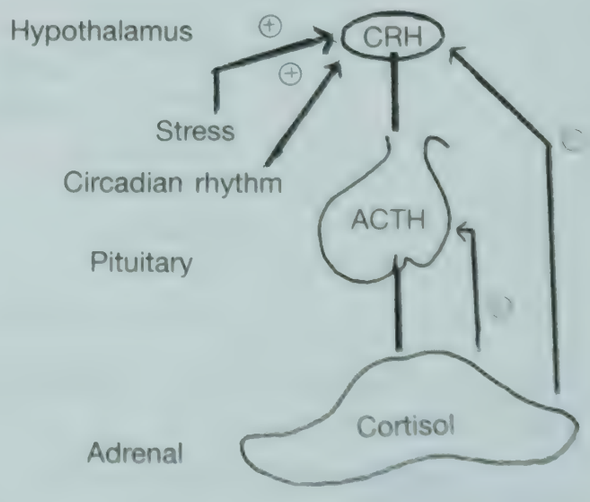


Fig 16.21 Regulation of cortisol secretion

and posture. The measurement of these peptides is technically difficult, and facilities for their measurements are not available in most laboratories in India. The plasma renin activity (PRA) is measured by incubating the patients serum to generate angiotensin I from the angiotensinogen present in the serum sample. The angiotensin I is measured by a radio-immunoassay.

Plasma levels: of cortisol, aldosterone, DHEA sulphate and androstenedione can be measured by radioimmunoassay.

Urine levels: Measurement of urinary excretion of adrenal steroids or their metabolites over 24 hours has the advantage of giving an integrated picture of steroid secretion, eliminating the effects of diurnal variation and variation induced by posture. Care must be taken to ensure adequate urine collection; simultaneously measured urinary creatinine helps to confirm proper collection.

The urine 17-OH corticosteroid assay measures cortisol, cortisone, tetrahydrocortisol, tetrahydrocortisone, and 11-deoxycortisol. A *urine free cortisol assay* is more useful since it only measures unbound cortisol and correlates well with elevated plasma cortisol.

The urine 17-ketosteroid assay measures steroids with a ketone group at C_{17}, that is, steroids with androgenic activity. In women 90 per cent of 17-ketosteroids are from the adrenal, while in men this figure is around 60–70 per cent.

Dynamic tests: Unlike the static tests mentioned above, these tests utilise physiological stimuli to either maximally stimulate hormone production when one wants to exclude a deficiency state, or to maximally suppress hormone production to document hypersecretion. These are intuitive tests, and such dynamic testing is used in all areas of endocrinology. For example, if one wanted to demonstrate a deficiency of cortisol production, the most convincing evidence would be to show that despite the application of a stimulus which normally increases the cortisol level, there is still no increase in cortisol. Two such stimuli are hypoglycemia, and an ACTH infusion. We know that cortisol is a counter-regulatory hormone in hypoglycemia and it increases in this state. If hypoglycemia is induced with insulin, the release of ACTH follows, and in turn cortisol is stimulated. Hence, this test examines the pituitary-adrenal axis, and if either of these is abnormal, submaximal cortisol levels will be obtained. The growth hormone level can also be measured, as this should also rise in response to hypoglycemia.

An *ACTH stimulation* test only measures the capacity of the adrenal gland's response to ACTH, hence will show inadequate cortisol release in adrenal disease. However, in long-standing pituitary disease the adrenals undergo atrophy due to chronic lack of ACTH stimulation, and in these cases a single ACTH injection will not elicit a response from the adrenals. For this reason a 24- or 48-hour synthetic ACTH infusion is used to separate a normal response from the partial response of secondary (pituitary-related) adrenal insufficiency, and the almost absent response of a primary (adrenal-related) adrenal insufficiency. Sometimes a single injection of synthetic ACTH (25 units) is used as a screening test: a normal response, that is, adequate rise in cortisol, implies a normal pituitary-adrenal axis, while a poor response needs to be further investigated.

Another dynamic test for the integrity of the pituitary adrenal axis is the *metyrapone test.* Metyrapone is a drug which inhibits the 11β hydroxylase in the adrenal gland, thereby preventing the conversion of 11-deoxycortisol to cortisol. Administration of this drug leads to lowering of cortisol levels, causing an increase in ACTH through the feedback mechanism. If the adrenals are normal, they respond to the increased ACTH by increasing 11-deoxycortisol production, which can be measured directly in

the blood, or in the urine as 17-hydroxysteroid. This normal response demonstrates an intact pituitary-adrenal axis.

When hypersecretion of adrenocortical hormones is suspected, tests attempting to suppress them are utilised. In suspected cortisol overproduction an attempt can be made to inhibit the ACTH secretion utilising normal feedback mechanisms (by giving a potent steroid like dexamethasone). In normal subjects a small dose of dexamethasone suppresses ACTH and this is reflected by a low plasma or urinary cortisol. Dexamethasone does not interfere with these assays since it is present in very small amounts. The standard *dexamethasone suppression test* involves giving 0.5 mg dexamethasone every 6 hours for two days, while collecting a 24-hour urine on the second day for cortisol estimation. In normal subjects the urinary cortisol is markedly reduced, while patients with hypersecretion of ACTH or ACTH-independent cortisol production will not show suppression of cortisol production in the standard dexamethasone test. Variations of this standard test are an overnight screening test or a high dose dexamethasone suppression test, and are described later in this chapter.

Mineralocorticoid reserve can be tested by sodium depletion and upright posture. Both of these should cause a rise in aldosterone secretion rates two-to-fourfold the basal rates. *Mineralocorticoid supressibility* can be tested by increasing extracellular volumes. This can be done by a saline infusion; one convenient protocol is to give 500 ml/hour of normal saline for four hours to suppress the aldosterone level.

As can be seen from the preceding description, there are various tests which can be utilised. The tests actually chosen depend on factors such as availability of laboratory facilities, convenience of the test, patient safety, and above all, the specific question which we want our test to answer.

ADRENOCORTICAL HYPERFUNCTION

When adrenal cortical hormones are hypersecreted distinct clinical syndromes are produced. Excess cortisol production causes Cushing syndrome, increased aldosterone production causes hyperaldosteronism, while excess adrenal steroid production causes virilisation in women.

Cushing Syndrome

The original description by Cushing was of a condition where an ACTH-producing pituitary adenoma caused bilateral adrenal hyperplasia and cortisol overproduction. This entity, which is the commonest cause of cortisol hypersecretion, is known as *Cushing's disease.* However, increased cortisol levels from any cause leads to a similar clinical picture, and all these conditions are grouped under the term *Cushing syndrome.* The various causes of Cushing syndrome are shown below:

The causes of Cushing syndrome are

1) Related to increased ACTH levels
   - Pituitary adenoma secreting ACTH–Cushing's disease
   - Ectopic ACTH secretion by tumours
2) ACTH independent cortisol production
   - Adrenal adenoma producing cortisol
   - Adrenal carcinoma producing cortisol
3) Exogenous glucocorticoid intake-associated with ACTH suppression

Pituitary adenomas secreting ACTH are often small, and are called microadenomas. By definition, pituitary tumours less than 10 mm in diameter are called microadenomas, whereas those larger than this are called macroadenomas. Pituitary hypersecretion of ACTH accounts for about 60 per cent of patients of Cushing syndrome. Another 15 per cent of patients have ectopic production of ACTH from a tumour, most commonly a bronchial carcinoma, thymic carcinoid, pancreatic cancer, or a bronchial

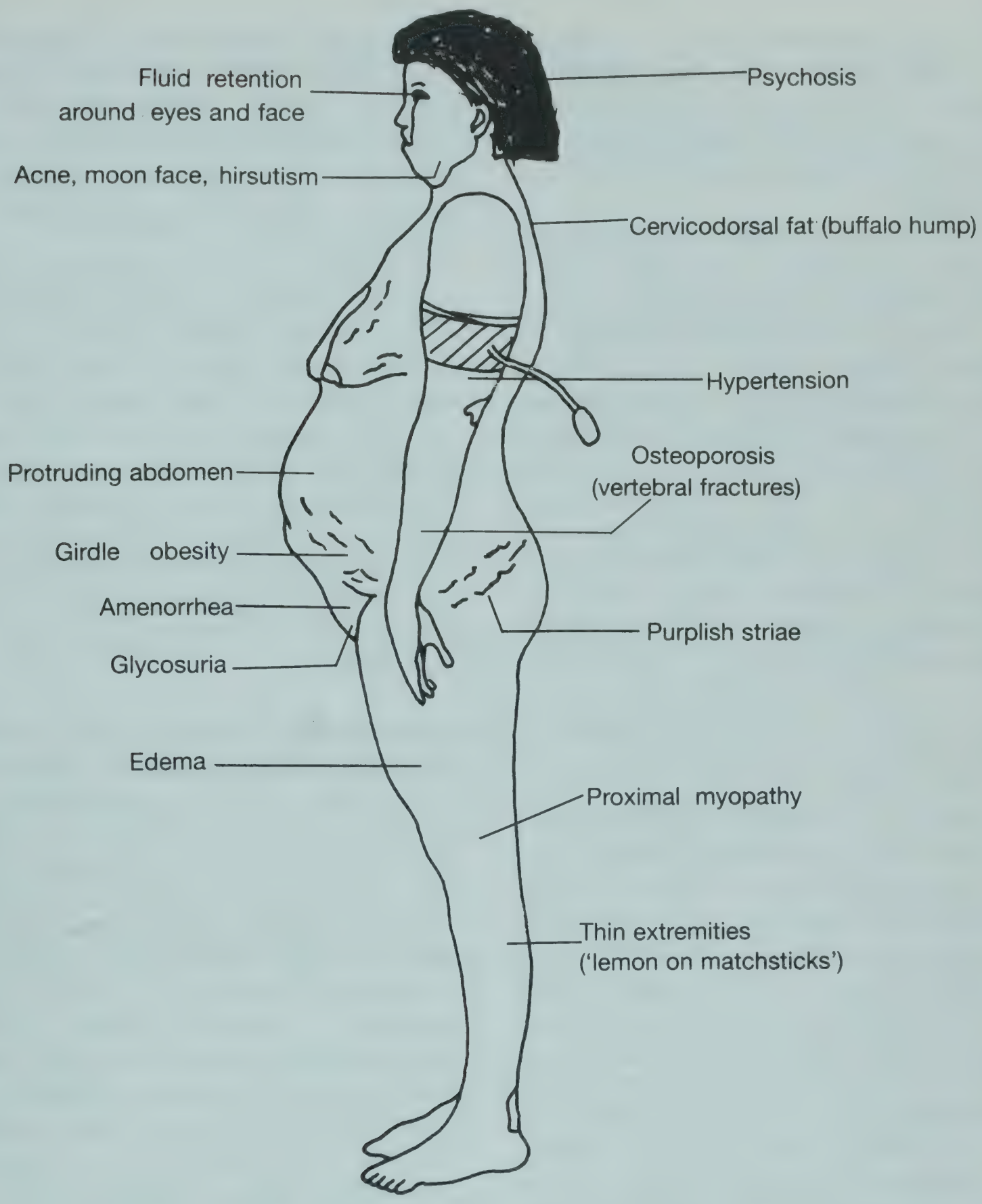


Fig 16.22 Clinical features of Cushing syndrome
(Note: Four features more specific of Cushing syndrome include cutaneous striae, thin extremities, proximal myopathy and osteoporosis.)

adenoma. All patients who hypersecrete ACTH from any cause will tend to have *bilateral adrenal hyperplasia,* which when chronic becomes nodular in appearance — the so-called *macronodular adrenal hyperplasia.* In the adrenal hyperplasia-associated cases of ACTH hypersecretion, the ACTH levels are often very high. This causes hypokalemia and metabolic alkalosis due to the effect of high ACTH on aldosterone production and the mineralocorticoid effects of the markedly elevated cortisol. The course of the illness in such patients may be so acute that they

may not have time to develop the classical physical characteristics of Cushing syndrome at presentation. Increase in skin pigmentation is another feature of ACTH hypersecretion, and when present in Cushing syndrome gives a clue to its etiology.

Primary adrenal tumours producing cortisol account for about 25 per cent of the cases of Cushing syndrome. Slightly less than half of these patients have an adrenal carcinoma, the rest have a benign adrenal adenoma. Hypersecreting adrenal tumours tend to suppress ACTH production. Malignant tumours are usually larger, and since they are less differentiated, they are inefficient hormone producers and may produce multiple hormones. For this reason, they are more frequently associated with adrenal androgen production and virilisation in addition to the features for Cushing syndrome.

Clinical features The clinical features of Cushing syndrome (Fig 16.22) common to all forms, irrespective of etiology, are the manifestations of chronic hypercortisolism. These include the typical body habitus resulting from the redistribution of adipose tissues characterised by truncal obesity, a rounded or *moon facies*, and increased fat deposition in the interscapular region — the so-called *'buffalo hump'*. In addition the patients lose fatty tissues from their limbs making these appear thin in proportion to the rest of the body. The skin is fragile with increased bruisability and striae. The striae are purplish in colour due to the visibility of the underlying subcutaneous tissue, unlike the striae of pregnancy or those associated with rapid weight change which are usually lighter in colour due to the associated fibrosis. There may be associated osteoporosis which manifests as vertebral fractures. There is muscular weakness most prominent in the proximal musculature; it is due to the effects of cortisol on the muscle. Patients may exhibit glucose intolerance, though overt diabetes mellitus occurs in less than a fifth of the patients. Hypertension is common. Mental changes are frequent and include irritability, emotional lability, depression and frank psychosis. If increased adrenal androgen production is also present it may lead to hirsutism, menstrual irregularities and virilisation in women.

In patients with a bronchial carcinoma producing ACTH, the course of the disease is so rapid that the patients do not have time to develop all the physical characteristics of Cushing syndrome. These patients often have very high cortisol levels and this leads to hypokalemia and alkalosis due to the weak mineralocorticoid effects of cortisol, and the increase in aldosterone which occurs secondary to the very high ACTH levels. The high ACTH also causes hyperpigmentation. Muscle weakness may be present as a result of the hypokalemia.

Investigations Laboratory tests are used to confirm the presence of hypercortisolism and to identify the reason for increased cortisol production.

Once exogenous intake of glucocorticoids has been excluded, increased secretion of endogenous cortisol can be demonstrated by a number of tests. The simplest *screening* test is the *overnight dexamethasone suppression test.* Normally, a single evening dose of dexamethasone suppresses the early morning cortisol peak by feedback inhibition on the ACTH secretion. The dose usually utilised is 1 mg of dexamethasone given at midnight. The 8 a.m. cortisol the next morning should be less than 5 μg/l. This test is very sensitive in picking up cases of hypercortisolism, but gives a false-positive result (that is, non-suppressibility of cortisol) in a few cases who do not have Cushing syndrome. Patients who give false-positive results include those under stress (such as an acute illness and hospital admissions), and people with obesity or depression. Alcoholics also have problems with non-suppressibility of

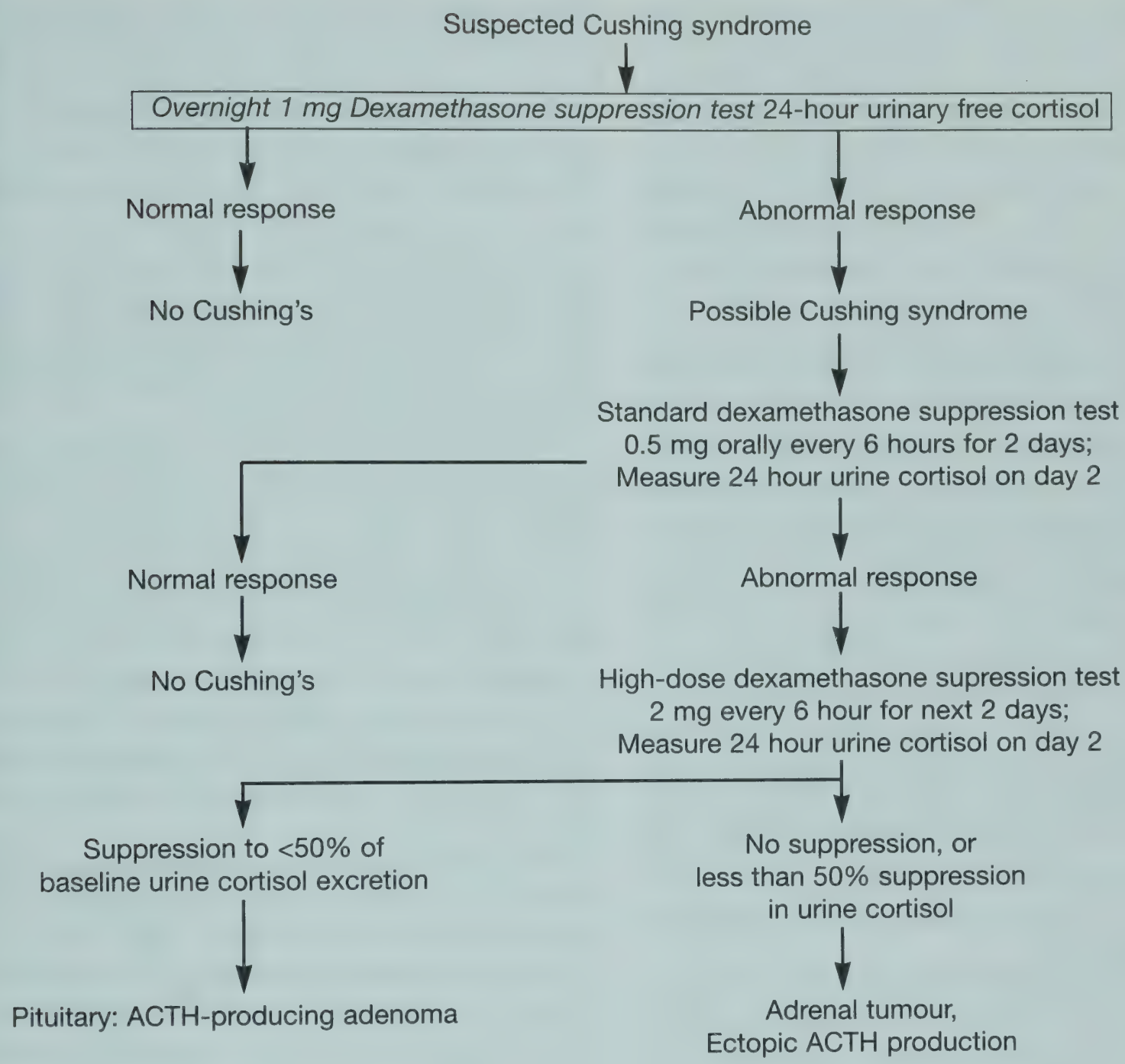


Fig 16.23 Diagnosis of Cushing syndrome—a laboratory approach

cortisol, and may sometimes even exhibit the physical characteristics of Cushing syndrome. Another screening test is the measurement of the 24-hour *urinary excretion of free cortisol* or 17-hydroxysteroids. If this is greater than 100 µg/day Cushing syndrome should be suspected. To a lesser degree this test is also prone to false-positive results for the categories of patients mentioned in the overnight dexamethasone supression test. Once the screening test is positive, the definitive diagnosis of Cushing syndrome is established by the *2 day low-dose dexamethasone suppression test.* For this, the patient is given 0.5 mg dexamethasone orally every 6 hours for 48 hours, and during the last 24 hours of the test, a urine collection is

done. In normal subjects the urine cortisol in this test should be less than 30 μg/day. If the urinary cortisol excretion is not suppressed to this level, the diagnosis of Cushing syndrome is made. To determine the etiology of Cushing syndrome the *high dose dexamethasone test* is frequently carried out. This can be done immediately following the low-dose test. For this test, 2 mg of dexamethasone is given every 6 hours for 48 hours and a urine collection is done on the second day, as in the low-dose test. With the high dose dexamethasone test, if the urine cortisol excretion is suppressed to less than the baseline level of urinary cortisol excretion, it suggests that the etiology of the Cushing syndrome is a pituitary adenoma producing ACTH. This is because pituitary adenomas are prone to some feedback inhibition with high doses of dexamethasone, whereas adrenal sources of cortisol or ectopic ACTH secretion do not respond at all to increasing doses of dexamethasone. It has been suggested that the level of suppression of the urinary cortisol be set at 50 per cent of baseline excretion[1] in the high dose dexamethasone suppression test, for the diagnosis of pituitary-dependent Cushing's disease (Fig 16.23).

Sometimes the distinction between Cushing's disease, that is, ACTH-producing pituitary adenoma and primary adrenal hypercortisolism is not clear with the above test. In such cases further testing needs to be conducted and a combination of tests may give an answer. Occasionally, however, the diagnosis is still unclear and there have been cases when a bilateral adrenalectomy to cure the hypercortisolism had to be performed when the etiology was unclear. Some of these patients then go on to develop an enlargement of a previously small pituitary adenoma, due to removal of any feedback inhibition from adrenal cortisol. The large amounts of ACTH produced by these adenomas may cause hyperpigmentation, while the enlarging pituitary may compress the optic chiasma. When this condition ensues, it has been described as *Nelson's syndrome.*

Other tests which help to distinguish the etiology of hypercortisolism include an ACTH measurement and the *metyrapone test.* An ACTH level is generally very high in ectopic ACTH production. In ACTH-secreting pituitary adenomas the ACTH may be elevated but frequently it is only marginally elevated or in the normal range. With adrenal neoplasms producing cortisol the ACTH is suppressed. The ACTH test is not readily available, and prone to assay variability.

Metyrapone is a drug which blocks cortisol synthesis, by interfering with the conversion of 11-deoxycortisol to cortisol. This leads to feedback stimulation of ACTH in cases of pituitary adenomas causing increase in 17-hydroxysteroid assay. In patients with an adrenal neoplasm, metyrapone blocks cortisol synthesis but the decrease in cortisol does not lead to an increase in pituitary ACTH production since this had been chronically suppressed by the previously high cortisol. In these patients the 17-hydroxysteroid urinary excretion will not increase from the baseline.

Once biochemical tests provide clues to the etiology of cortisol overproduction, imaging studies help to localise the abnormality. ACTH-producing microadenomas are often difficult to visualise even on CT scans. MRI may be superior to CT scan in these patients. In centres where facilities are available, sampling of blood from the petrosal sinus to show a gradient between this and peripheral blood ACTH, helps

1 By baseline cortisol excretion, we mean the 24-hour urinary cortisol carried out without any dexamethasone. The criteria for the interpretation of the high dose dexamethasone test utilising suppression to at least 50% of the baseline have the potential to miss some patients with a pituitary microadenoma who suppress to some extent with the high dose dexamethasone, though the suppression is not over 50% of the baseline. Many believe that any suppression of the baseline urinary cortisol with the high dose dexamethasone is significant and suggests ACTH-secreting pituitary adenoma. It should be kept in mind that this suppression should be significant in that it should take into account the variations in sample collection and the assay variability.

to localise the source of excess ACTH to the pituitary. Abdominal imaging studies help to localise adrenal tumours. Adrenal carcinomas are usually larger, and more frequently show increased levels of adrenal androgens than benign adenomas.

Treatment Treatment depends on the underlying cause. Pituitary adenomas are removed by the transsphenoidal route. Benign adrenal adenomas are treated by adrenalectomy. In cases where ACTH overproduction is demonstrated and the source for this is not apparent but is thought to be from the pituitary, transsphenoidal exploration may be done. Alternatively, bilateral adrenalectomy may be performed and though cure is certain with this, there is a risk of Nelson syndrome, and the need for lifelong mineralocorticoid and glucocorticoid replacement therapy. In patients in whom surgical therapy is not desirable, such as those with adrenal cancers, *medical adrenalectomy* can be accomplished by drugs which inhibit synthesis of steroids by the adrenal. These drugs include ketoconazole, mitotane and aminoglutethimide. Hypoadrenalism is a risk with all these agents, so replace ment therapy may have to be instituted. Radiation of the pituitary is an alternative for patients who have a demonstrable pituitary hypersecretion of ACTH, but who are not surgical candidates. This takes months to have an effect; meanwhile drugs to inhibit adrenal steroidogenesis may be given.

Aldosteronism

Excess aldosterone production may be due to a defect within the adrenal gland such as an aldosterone-producing adenoma. This is known as *primary aldosteronism. Secondary aldosteronism* occurs when the adrenals respond to external stimuli to produce more than normal amount of aldosterone, the adrenals themselves being normal.

Primary aldosteronism (Conn syndrome)

This is an uncommon disorder, and presents as hypertension associated with hypokalemia. Less than 1 per cent of patients with hypertension have this disorder. The commonest cause of primary aldosteronism is a solitary adrenal adenoma, but some patients have bilateral adrenal hyperplasia as the underlying cause. Adrenal carcinoma is a rare cause of aldosteronism.

Aldosterone acts on the distal renal tubule and collecting ducts to retain sodium in exchange for potassium and hydrogen ion. This leads to expansion of the intravascular volume and development of hypertension. Diastolic hypertension is typical. Hypokalemia leads to muscle weakness, and polyuria results due to reduction in the concentrating ability of the kidney. This leads to polydipsia. The hypokalemia is associated with ECG changes such as prominent U waves and cardiac arrhythmias. There is also associated metabolic alkalosis. Though aldosteronism is associated with increased total body sodium and water, edema is absent, and this is thought to be due to an 'escape' mechanism from the effects of aldosterone on the renal tubule.

The diagnosis should be suspected in a hypertensive patient who is hypokalemic even when not on a potassium-wasting diuretic, or while on a potassium-sparing diuretic. Hypersecretion of aldosterone should be demonstrated, particularly when the patient is loaded with salt and water which normally suppresses aldosterone. It should also be demonstrated that the plasma renin activiy is suppressed to prove a primary adrenal etiology (see section on adrenal physiology).

Other conditions which present with hypertension and hypokalemia may be confused with primary aldosteronism. These include deoxycortisone-secreting adenoma. Deoxycortisone is also a mineralocorticoid (Fig 16.19), but aldosterone levels in these patients is low or normal. Similarly in 11- or 17-hydroxylase enzyme defects in cortisol biosynthesis (Fig 16.19), there is overproduction of the intermediate, preceding the defective step due to

excess ACTH production resulting from cortisol deficiency. This intermediate, 11-deoxycortisone, also has mineralocorticoid activity. These patients respond well to exogenous glucocorticoids since this terminates excess ACTH production and normalises the hypertension and hypokalemia. Licorice ingestion also mimics hyperaldosteronism clinically. Licorice is a substance added to confectionary and tobacco and is popular in Europe. It causes increased mineralocorticoid activity, but aldosterone levels are suppressed.

Once the diagnosis of primary aldosteronism is established by laboratory tests, the etiology can be established by abdominal imaging studies and bilateral catheterisation of the adrenal vein to demonstrate differences in aldosterone production between the adrenals. If a unilateral adenoma is visualised on an imaging study, or if venous catheterisation shows the secretion of aldosterone from one adrenal to be much more than from the other one, the diagnosis is a unilateral adenoma. If both adrenals show hyperplasia, and demonstrate equally high aldosterone production, the diagnosis is bilateral adrenal hyperplasia.

The treatment of a solitary adenoma is usually surgical excision. Medical therapy is used prior to surgery, and in patients with bilateral adrenal hyperplasia. Medical therapy consists of the addition of potassium-sparing diuretics, for example, spironolactone, triamterene or amiloride, to the antihypertensive treatment.

Secondary Aldosteronism

Secondary aldosteronism is due to increased activation of the renin-angiotensin system. It may be associated with a hypertensive state as in renal artery stenosis, and in primary excess renin production. It also occurs without hypertension in states of apparent or true arterial hypovolemia as occurs in congestive heart failure, cirrhosis and nephrotic syndrome. In these conditions edema is often present. A distinct type of hyperaldosteronism occurs without edema or hypertension, due to juxtaglomerular hyperplasia in the kidney and consequent renin overproduction. This condition is known as *Bartter syndrome,* and is associated with an increase in renal production of prostaglandins, hypokalemia and metabolic alkalosis. The underlying defect causing this condition is unclear.

Adrenal Androgen Overproduction

Androgen excess from the adrenals, occurring in the postpubertal period, causes signs of virilisation only in women since in men the testes are the main source of androgens at this stage. In the prepubertal stage, adrenal androgen excess causes precocious puberty in males. In females, androgen excess early in development leads to development of ambiguous genitalia, while at a later stage it may cause precocious puberty and virilisation.

Virilisation in a woman is another word for masculinisation and is much more than just hirsutism. Besides hirsutism, which may be the first feature, it includes muscular hypertrophy, deepening of voice, clitoromegaly and acne. Hirsutism by itself occurs in many women without evidence of androgen excess, but the hirsutism of virilisation is associated with increased hair growth in the beard and moustache area and the male pattern of pubic hair growth.

Adrenal androgen overproduction may be due to adrenal adenoma or carcinoma. It also occurs due to enzymatic defects in the adrenals when glucocorticoids or mineralocorticoids cannot be adequately synthesised. This leads to all the precursor steroids being directed towards androgen synthesis. Moreover, the low glucocorticoids lead to a compensatory increase in ACTH secretion which leads to adrenal hyperplasia and further drives the glands to produce more androgens. This condition is known as congenital adrenal hyperplasia. Many enzyme defects are known to cause congenital adrenal hyperplasia, the commonest being a

1-hydroxylase deficiency. All these disorders ead to virilisation in the female, and the other eatures depend on whether associated lucocorticoid or mineralocorticoid deficiencies re present. If the defect is complete, females nay be born with ambiguous external genitalia female pseudohermaphroditism). Sometimes he defect is partial and may not be recognised ill adulthood. The treatment is with exogenous lucocorticoids to shut off ACTH production hereby reducing adrenal androgen production.

Adrenocortical Hypofunction

Hypofunction of the adrenal cortex may either e due to an intrinsic adrenal defect, when it is alled *primary adrenocortical deficiency,* or due o a defect in ACTH secretion by the pituitary, when it is called *secondary adrenal insufficiency.*

Primary adrenocortical insufficiency: Addison's disease

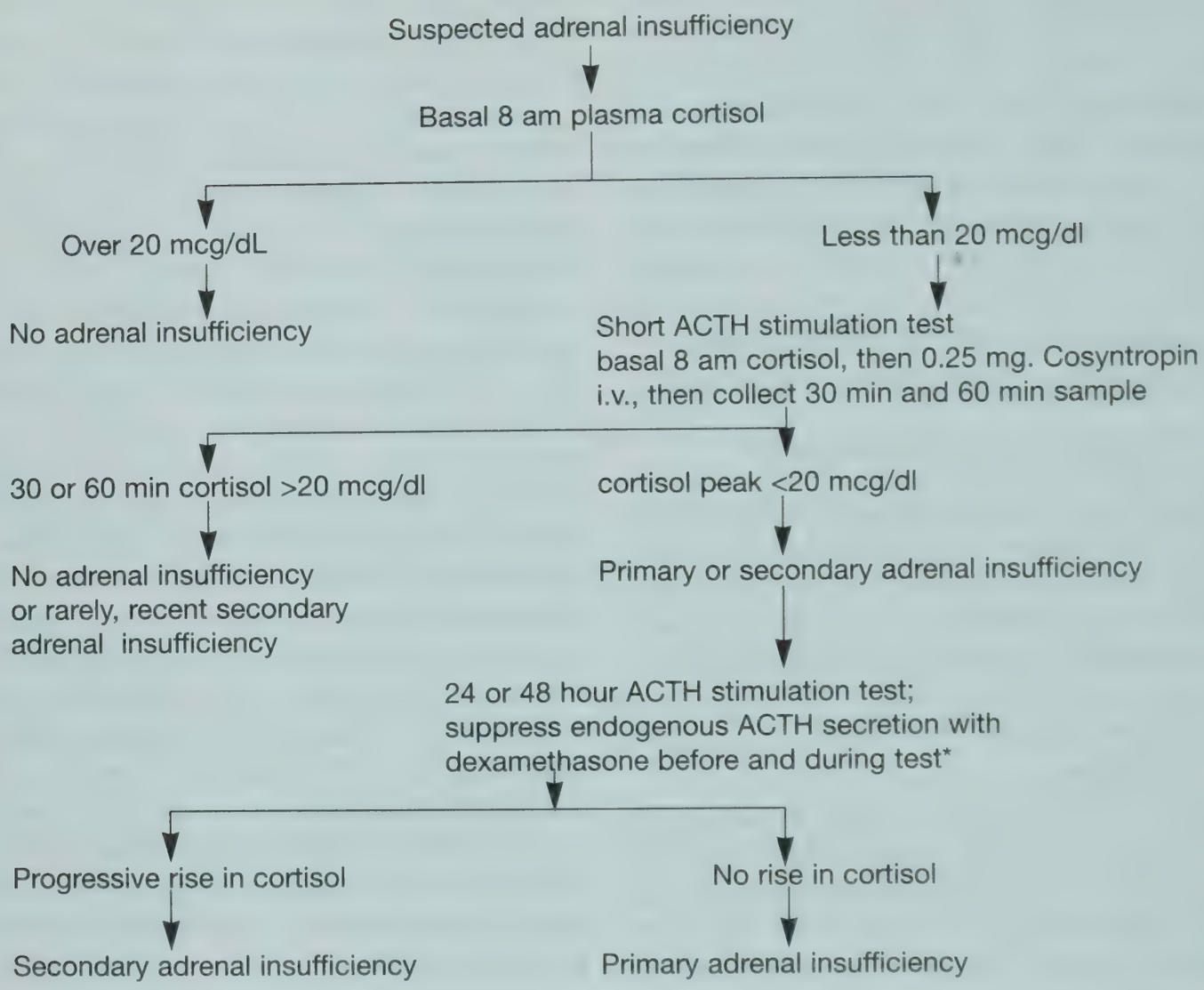
Addison's disease occurs from progressive destruction of the adrenals. Over 90 per cent of adrenal function must be destroyed before adrenal insufficiency manifests itself. The signs of primary adrenal deficiency occur due to both glucocorticoid and mineralocorticoid deficiency. The increase in ACTH which occurs in response to these deficiencies also causes the symptom of hyperpigmentation. ACTH is formed from the same precursor molecule as melanocyte stimulating hormone (MSH) and a part of the peptide structure is common to both hormones. An increase in ACTH leads to stimulation of the melanocytes in the dermis which is the reason for the hyperpigmentation seen with ACTH excess.

An important cause of Addison's disease in India is tuberculous infection of the adrenal gland. The granulomas and necrosis associated with tuberculosis destroy much of the gland. Frequently, active tubercular infection can be demonstrated elsewhere in the body, but it may be clinically latent. In the early stage of the disease the glands are enlarged, but as the disease progresses the glands become fibrosed with foci of caseation. Calcification is common, and may be observed on an abdominal X-ray.

Other causes of adrenal destruction include autoimmune destruction, bilateral adrenal hemorrhage, tumour metastases, and other granulomatous infections. Sarcoid and amyloidosis are rare causes of adrenal destruction. Adrenal hemorrhage occurs in association with hypotension and sepsis and is also a complication of anticoagulation therapy. Patients with autoimmune destruction of the adrenals may have other organ-specific autoimmune diseases such as insulin-dependent diabetes mellitus, Hashimoto's thyroiditis, and premature ovarian failure. *Autoimmune adrenalitis* is more common in the Caucasian population than in Indians; the reason for this is unclear but may be related to genetic differences. Acquired Immunodeficiency Syndrome (AIDS) may be associated with adrenal destruction due to cytomegalovirus or cryptococcus infections or due to involvement of the adrenals with Kaposi's sarcoma. Medications such as ketoconazole may also interfere with adrenal function.

The symptoms of adrenal failure include progressive fatiguability with generalised weakness. Gastrointestinal symptoms are prominent and include anorexia, loss of taste, nausea and vomiting, and weight loss. Patients frequently have abdominal pain with diarrhea or constipation, and may crave for salt. Depletion of salt and water leads to hypovolemia and orthostatic hypotension which may cause postural dizziness. Hyperpigmentation is an associated feature, and should be looked for on mucosal surfaces such as on the buccal mucosa, and the palms and knuckles of the hands. Patients are irritable and may have personality changes.

Laboratory findings include the typical electrolyte abnormalities of mineralocorticoid deficiency, that is, hyponatremia and hyperkalemia. Due to the absence of gluconeogenetic effects of cortisol, patients may have hypo-



** Details of this test can be found in a specialist endocrinology text.*

Fig 16.24 Laboratory approach to the investigation of adrenal insufficiency

glycemia. Hypercalcemia occurs due to poorly understood reasons. Eosinophilia occurs, which is the reverse of what one sees with Cushing syndrome. The serum cortisol is low, as is the 24-hour urinary cortisol excretion. However, with mild adrenal insufficiency these levels may overlap with the normal range. In these cases it can be demonstrated that the plasma and urinary cortisol do not respond to ACTH stimulation. Though all patients of primary adrenal insufficiency will not respond to a single injection of ACTH, some patients with secondary adrenal insufficiency will also not respond to the single ACTH injection. This is because their adrenals atrophy due to chron deprivation of ACTH stimulation. T differentiate these two groups of patients, 24 hour or even 48 hour ACTH stimulation te may have to be used. Patients with secondar adrenal insufficiency will respond to th prolonged ACTH test by demonstrating a rise i cortisol. Patients with secondary adren insufficiency of recent onset (for example wit recent pituitary destruction), will have relative normal adrenals which respond well to the sing ACTH injection with a rise in cortisol levels. scheme for the tests in adrenal insufficiency given in Fig 16.24.

All patients of Addison's disease should receive hormone replacement with glucocorticoids and mineralocorticoids. Patients who are very sick should receive treatment immediately rather than wait for the results of the laboratory tests. The ACTH stimulation test can often be performed a day or two after treatment is commenced; in such cases treatment should be with dexamethasone since it does not interfere with the cortisol assay. Glucocorticoids may be given as hydrocortisone, prednisone or dexamethasone. The usual dose of hydrocortisone is 30 mg/day which is equivalent to 7.5 mg of prednisone or 0.5 mg dexamethasone. To try and mimic the normal diurnal rhythm, two-thirds of the daily dose of hydrocortisone is given in the morning while a third is given in the evening. Both dexamethasone and prednisone are longer acting and may be given as a single daily dose. Since the adrenal glands increase endogenous steroid production during stress, patients of adrenal insufficiency who are dependent on exogenous steroids need to increase their steroid dose during periods of stress. During maximal stress such as major surgery, doses of hydrocortisone as high as 300 mg/day in divided doses may be given. This may have to be given parenterally if the patient is unable to take it orally. This dose is rapidly decreased to maintenance dose as the stress abates. For minor illnesses doubling the usual glucocorticoid dose is sufficient. Mineralocorticoid replacement is given by the administration of a synthetic derivative, fludrocortisone, in the dose of 0.05 to 0.1 mg daily. To follow-up the patient for adequacy of therapy or overtreatment, periodic measurements of body weight, serum potassium, and blood pressure is useful. The feeling of clinical wellbeing is an important indicator of appropriate therapy.

Secondary Adrenocortical Insufficiency

Secondary adrenocortical insufficiency is due to deficient ACTH secretion by the pituitary. It may occur due to hypopituitarism from any cause such as a tumour, or pituitary apoplexy. It is associated with symptoms of deficiencies of multiple pituitary trophic hormones. Selective ACTH deficiency is seen in patients who have been administered exogenous glucocorticoids over prolonged periods for therapeutic reasons. In such patients if glucocorticoids are stopped abruptly, secondary adrenal insufficiency develops as the pituitary is incapable of restoring ACTH secretion rapidly. In all cases of secondary adrenal insufficiency aldosterone levels are normal, since the secretion of this hormone does not depend on ACTH stimulation. For this reason, hypotension, hyponatremia and hyperkalemia (which are mineralocorticoid effects), are not seen in this condition though the other symptoms are similar to those of primary adrenal insufficiency. *Tertiary adrenal insufficiency* is a rare condition and occurs when there is an abnormality of the hypothalamus preventing CRH release.

Addisonian (adrenal) crisis

Adrenal crisis is an endocrine emergency as it is a life-threatening condition if not treated promptly. It can occur in a patient of chronic adrenal insufficiency and is usually precipitated by a period of increased stress (such as an infection or trauma), especially when the dose of replacement glucocorticoids is either not taken or not increased. It can also occur secondary to acute adrenal insufficiency which occurs in conditions such as sepsis. A distinct form of acute adrenal insufficiency occurs in children with meningococcal septicemia, which may be associated with adrenal hemorrhage and is known as the *Waterhouse-Friderichsen syndrome.*

The presentation of a patient in adrenal crisis is with intensification of symptoms of adrenal insufficiency such as increased nausea, vomiting, abdominal pain and hypotension. The patient may be febrile. Typical laboratory abnormalities of adrenal insufficiency are present. The management includes a search for a precipitating cause, fluid replacement, and intravenous

glucocorticoids. Intravenous glucose and saline may need to be given to correct volume deficits and sodium depletion and hypoglycemia. Since large doses of cortisol have some mineralocorticoid effect, mineralocorticoids may not be needed initially. To prevent such crises patients of known adrenal insufficiency should be taught how to inject dexamethasone intramuscularly in case of an illness which prevents them from taking oral medications.

Hypoaldosteronism

Isolated hypoaldosteronism is rare. It can be seen in association with hyporeninism, which may be inherited or acquired due to conditions such as diabetes mellitus. In such patients low renin and aldosterone levels are seen even during provocative testing with stimuli such as upright posture and salt depletion, both of which increase aldosterone levels. Sometimes hypoaldosteronism is seen when there is a defect in the biosynthetic pathway, and in these cases renin levels are elevated. Transient hypoaldosteronism can be seen after removal of an aldosterone producing tumour, as the contralateral normal adrenal cortex is suppressed. In rare cases, prolonged heparin therapy is associated with aldosterone deficiency.

In all these cases hyperkalemia is the predominant feature, with hyponatremia occurring when salt intake is low. Treatment is with mineralocorticoid replacement.

Adrenal medulla-pheochromocytoma

Adrenal medullary hypofunction, as may occur after adrenalectomy or destruction by metastases or hemorrhage, does not produce any definite clinical abnormalities. The only significant clinical entity resulting from adrenal medullary pathology is a pheochromocytoma or a tumour of the *chromaffin cells*. These tumours produce and secrete catecholamines, and their clinical manifestations result from catecholamine excess. Hypertension is the major clinical manifestation. Though pheochromocytomas account for only 0.1 per cent of all hypertensive patients, it is a correctable cause of high blood pressure.

Pheochromocytomas are unilateral in 80 per cent of the cases; 10 per cent are bilateral and 10 per cent are extra-adrenal. Extra-adrenal pheochromocytomas occur commonly in the abdomen, but can occur in the chest or wherever chromaffin cells are present. Most pheochromocytomas are benign, but about 10 per cent are malignant. In less than 5 per cent, pheochromocytoma is inherited as an autosomal dominant trait in the *multiple endocrine neoplasia type 2* (MEN 2) syndrome. These patients may have parathyroid adenomas, and medullary carcinoma of the thyroid in association with the pheochromocytoma. MEN 2 should be suspected in any patient with a family history of pheochromocytoma or bilateral pheochromocytomas.

Most pheochromocytomas synthesise and release both epinephrine and norepinephrine. Extra-adrenal pheochromocytomas synthesise norepinephrine exclusively. Increased production of dopamine may be seen in malignant tumours. The biosynthetic pathway for catecholamines is outlined in Fig 16.25.

Pheochromocytoma can present at all ages but is most common in young adulthood and middle age. It should be suspected in patients who have a history of episodic hypertension, frequent hypertensive crises, and severe hypertension which is difficult to control with conventional antihypertensive therapy. In over half of the patients the hypertension is sustained while in the others it is episodic. A classic feature of this disorder is paroxysms of hypertension, associated with sweating, palpitations and headache. Though the presence of all these features makes the diagnosis of pheochromocytoma very likely, only half of all patients have these paroxysms. Patients may exhibit other signs of increased metabolic rate such as weight loss and sweating. The catecholamine excess causes tachycardia, and may predispose to supraventricular arrhythmias

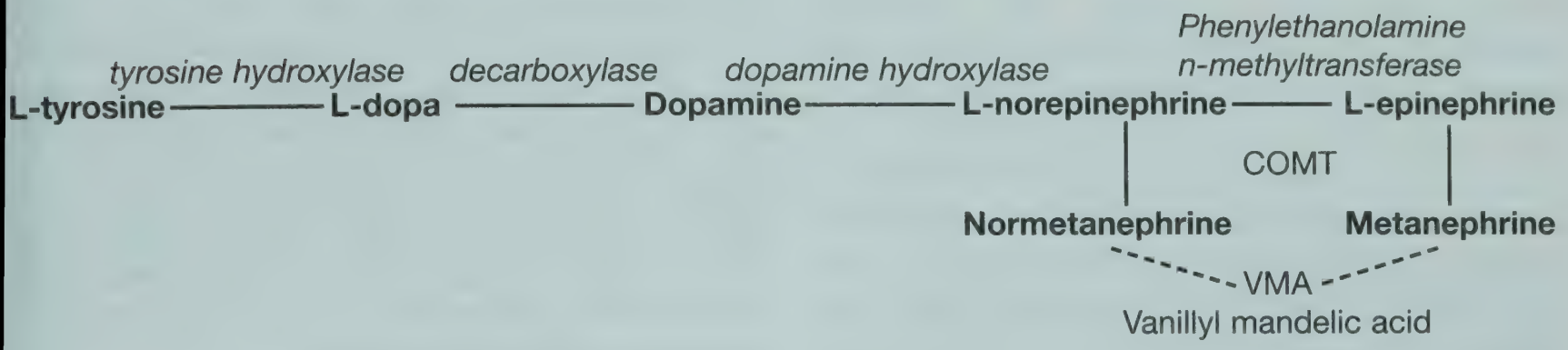


Fig 16.25 Biosynthesis and degradation of catecholamines

and premature ventricular beats. There may be associated glucose intolerance. Drugs which increase the release of catecholamines from the tumour or which reduce catecholamine uptake by nerve endings may cause such paroxysms, and these include opiate analgesics, methyldopa and tricyclic antidepressants.

The diagnosis of a pheochromocytoma can be established by demonstrating an excess excretion of catecholamines in the 24-hour urine collection, and by demonstrating a tumour in an adrenal or extra-adrenal site. The urine collection should be made when the patient is at rest and not under stress, since stress can elevate catecholamine production and excretion. Since different tumours secrete different metabolites, it is preferable to measure two or three different chemicals. The catecholamines commonly measured are epinephrine, and sometimes norepinephrine, and their metabolites *vanillyl-mandelic acid* (VMA) and *metanephrines*. Elevations of epinephrine excretion may occur with drugs such as methyldopa, levodopa, and labetalol. Monoamine oxidase inhibitors increase metanephrine excretion but decrease VMA excretion. Propranolol interferes with metanephrine assays. Before sending the urine specimen it is advisable to contact the laboratory to obtain a list of medications which interfere with the interpretation of the assay. Plasma catecholamines are less useful in the diagnosis, as their assays are less well-standardised and are prone to the same drug interactions as the urine assays. Plasma catecholamine levels before and after clonidine have been used to support the diagnosis of pheochromocytoma. In normal subjects and hypertensives who do not have a pheochromocytoma, clonidine reduces the catecholamine levels, while in patients with pheochromocytoma, clonidine fails to suppress plasma catecholamine levels. Glucagon has little effect on catecholamine levels in subjects without a pheochromocytoma, but in people with a pheochromocytoma, catecholamine levels rise, and may precipitate a hypertensive crisis. For this reason, the glucagon provocative test should be only used with careful clinical monitoring of blood pressure, and phentolamine should be available to treat any crises. This test is not recommended unless absolutely essential.

Localisation of the tumour can be detected with a CT scan or an MRI scan. The MRI shows a characteristic bright appearance on T2-weighted images due to the vascularity of the tumour. In centres where CT or MRI is unavailable, angiography of the adrenals will demonstrate the tumour. In general, localisation of the tumour by imaging techniques should only be done after biochemical tests are suggestive of the diagnosis, due to the fact that the finding of a non-functioning incidental adrenal mass is not uncommon. Agents such as ^{131}*I-Meta-iodobenzylguanidine* (MIBG), have been used to scan for pheochromocytomas since they take up this agent. Use of this agent is as yet investigational.

The management of a patient with pheochromocytoma includes the medical treatment of hypertension with drugs, and ultimately the surgical removal of the tumour. The drugs used to treat hypertension in pheochromocytoma are mainly alpha adrenergic blocking drugs. This is because alpha adrenergic receptors on the vasculature are important for catecholamine-mediated vasoconstriction and hypertension. Alpha receptor blocking drugs include the long acting phenoxynbenzamine and the short acting phentolamine. Prazosin, an alpha blocking drug may also be used. Phenoxybenzamine is most widely used for this condition; the starting dose is 10 mg/day, which is increased in 10 mg doses till blood pressure control is achieved. Since surgery causes release of a large amount of preformed catecholamines in the patient, preoperative blockade of alpha receptors is essential, and generally a two week course of these drugs is given. Beta-blockade may be added to reduce the cardiac manifestations of the increased catecholamines, but should be added after the alpha blockade is begun. This is because beta receptors in the skeletal muscle vasculature are important for vasodilation, and commencing beta-blockade first may lead to worsening of the hypertension. Labetalol is both an alpha- and beta-blocker, and it has been suggested that it may be used for the preoperative management of pheochromocytoma. However, its actions on the alpha receptor are weak, and it is not recommended that this agent be used by itself for this purpose.

Surgery carries with it a risk for hypertensive crises, arrhythmias, and postoperative hypotension (due to the removal of the vasoconstricting stimulus of the catecholamines). The latter responds best to volume expansion. Hypertension may be managed with intravenous phentolamine in the dose of 1–5 mg. Propranolol may be given intravenously (dose from 0.5–1 mg.) for the treatment of tachycardia and ventricular ectopy. Lidocaine should be at hand for arrhythmias, and nitroprusside may be used for hypertension that does not respond to phentolamine. Surgery for pheochromocytoma should be done at a centre with experience in the management of such patients.

Evaluation of asymptomatic adrenal masses

About 10 per cent of subjects at autopsy have incidentally discovered adrenal masses which were clinically silent during life. With the increased use of abdominal imaging techinique such as the CT scan, more patients with such masses *(incidentalomas)* are being detected during life. Evaluation of such patients proves to be a dilemma. A clinical examination should be carried out to exclude signs of hypercortisolism and hypertension. If the patient is hypertensive laboratory evaluation to exclude pheochromocytoma and hyperaldosteronism are justified. Since most of these masses will be non-functioning, it is probably not worthwhile to carry out extensive laboratory tests to exclude all adrenal conditions. However, a test for serum potassium (to exclude hyperaldosteronism) is probably worthwhile. It has been suggested that if the mass is larger than 5 cm, evaluation be carried out to exclude adrenal carcinoma. This would include a repeat CT scan to look for growth of the mass. Of the clinically significant incidentalomas, the common ones are (in order of frequency) aldosterone-producing adenoma, pheochromocytoma and a cortisol-secreting adenoma.

KEY CONCEPTS

Adrenal insufficiency

- Adrenal insufficiency may be *primary* (Addison's disease; increased ACTH), *secondary* (hypopituitarism; low ACTH) or *tertiary* (hypothalamic dysfunction). Causes of Addison's disease include granulomatous destruction (TB, CMV, fungal), autoimmune disease, and adrenal hemorrhage. Over 90 per cent of the adrenals must be destroyed before hormonal insufficiency becomes clinically evident.
- Clinical features are related to deficiency of mineralocorticoids, glucocorticoids or adrenal androgens. Compensatory ACTH elevation in Addison's disease results in hyperpigmentation of buccal mucosa, skin over knuckles and scars. Mineralocorticoid deficiency results in orthostatic hypotension, and salt craving. Complaints related to glucocorticoid deficiency include lethargy, weight loss, fatigue, abdominal pain and personality changes. Adrenal androgen deficiency results in loss of axillary and pubic hair.
- Laboratory investigations reveal hyperkalemia, hyponatremia, a mild metabolic acidosis, eosinophilia, and low voltage ECG complexes. Abdominal skiagram may reveal adrenal calcification. Low plasma aldosterone levels with increased plasma renin activity is suggestive of adrenal insufficiency. Serum cortisol levels are low and do not increase on the ACTH stimulation test.
- Management consists of indefinite steroid replacement along with fludrocortisone (for mineralocorticoid replacement).
- Acute adrenal crisis results in nausea, abdominal pain, hypotension and peripheral vascular collapse. It is treated with intravenous fluids (glucose and saline) and parenteral hydrocortisone.

Congenital adrenal hyperplasia

- CAH results from one of several enzymatic defects in the cortisol biosynthetic pathway. Cortisol deficiency results in increased ACTH levels; elevated ACTH causes overproduction of those steroids whose synthesis is unaffected (principally adrenal androgens).
- CAH often presents with precocious puberty in males and as ambiguous genitalia or virilisation in women.
- 21-hydroxylase deficiency results in a salt losing syndrome (hypoaldosteronism), while 11-hydroxylase deficiency manifests with systemic hypertension (mineralocorticoid excess). 17-hydroxylase results in hypertension, and combined androgen and estrogen deficiency; this results in amenorrhea in women and ambiguous genitalia in men.
- Measurement of urinary 17-ketosteroids, pregnanetriol and plasma cortisol and androgens helps identify the specific enzyme deficiency.

Cushing syndrome

- In this condition there is an increase in plasma cortisol levels due to endogenous secretion by a pituitary adenoma (65%; called Cushing disease), an adrenal adenoma (10%), an adrenal carcinoma (10%) or due to ectopic production of ACTH (15%; e.g., small cell lung cancer). Exogenous administration can also result in a Cushingoid appearance.
- Clinical manifestations include truncal obesity, hypertension, moon facies, a buffalo hump, thin extremities, cutaneous striae, proximal myopathy and skeletal osteoporosis. Ectopic ACTH-secreting tumours result in cutaneous hyperpigmentation and episodes of hypokalemic alkalosis; they may not result in the typical physical appearance.
- Increased levels of plasma cortisol despite dexamethasone suppression, a loss of the normal diurnal secretory rhythm, and elevated urinary free cortisol levels suggest a diagnosis of Cushing syndrome. ACTH levels help differentiate etiologies; whereas ACTH levels are normal or low in adrenal tumours, they are moderately elevated in patients with a pituitary adenoma, and markedly so in patients with an ectopic ACTH-secreting tumour. A CT/MRI scan helps identify adrenal and pituitary neoplasms.
- The *low* (0.5 mg every 6 hours) and the *high dose* (2 mg every 6 hours) *dexamethasone suppression tests* help differentiate the potential etiologies:
  - Suppression of plasma cortisol (<5μg/dl) with both the low and the high dose of dexamethasone is the normal response.
  - Suppression of plasma cortisol with high dose but not with low dose dexamethasone suggests Cushing's disease (pituitary tumour).
  - Suppression with neither the low nor the high dose dexamethasone test suggests an adrenal tumour or ectopic ACTH secretion.
- Management depends on the source of hypercortisolism: surgery for pituitary or adrenal adenomas; surgery, if feasible, or antiadrenal drugs (metyrapone, ketoconazole/spironolactone) for ectopic ACTH-secreting tumours.

Conn syndrome

- In this condition there is increased production of aldosterone which is independent of the renin-

angiotensin system. A majority of cases are due to a unilateral adrenal adenoma (66%; young, M:F=1:2); other causes include bilateral adrenal hyperplasia (older, M=F), and adrenal carcinoma.

➢ Mineralocorticoid excess results in sodium retention and potassium loss. Yet there is no edema (*escape*). Sodium retention results in hypertension (<1% of all hypertension) while potassium loss manifests as polyuria, polydipsia and proximal myopathy. Conn syndrome must be suspected in any hypertensive who is hypokalemic but not on steroids or diuretics.

➢ Laboratory investigations reveal low serum potassium, mild hypernatremia and a saline-resistant metabolic alkalosis. High plasma aldosterone levels with low renin levels are diagnostic of Conn syndrome. Urinary 18-OH corticosteroids differentiate an adrenal adenoma (>100 ng/dl) from hyperplasia. A CT/MRI scan can identify large tumours.

➢ Management depends on the etiology; surgery for adrenal adenomas, spironolactone for bilateral adrenal hyperplasia.

Pheochromocytoma

➢ This is a catecholamine-secreting tumour of chromaffin tissues; adrenal tumours secrete epinephrine more than norepinephrine and the converse applies to extra-adrenal tumours. The tumour may be a feature of MEN type 2.

➢ About 10 per cent of tumours are bilateral, 10 per cent are familial, 10 per cent are extra-adrenal, and 10 per cent are malignant.

➢ Symptoms may be paroxysmal (attacks) or sustained (more common). Important features include headache, weight loss, hypertension (but with postural hypotension), tachycardia, palpitations, increased sweating and hyperglycemia (the triad of headache, palpitation and sweating is important). Occasionally, patients present dramatically with sudden collapse during surgery or pregnancy.

➢ Diagnosis is with urinary metanephrines, VMA or with plasma catecholamines. A clonidine suppression test may be useful (plasma catecholamines fall <2000pg/ml 3 hours after 0.3 mg of clonidine normally, but not in patients with pheochromocytoma). A CT/MRI scan may reveal the tumour; alternately, a metaiodobenzylguanidine scan (MIBG) can image the adenoma.

➢ Definitive treatment consists of surgical excision; preoperative preparation includes initial alpha-blockade (phentolamine, phenoxybenzamine) followed by beta-blockers. Metyrosine (tyrosine hydroxylase inhibitor) may be used as an adjunct.

16.8 Diabetes mellitus

Diabetes mellitus comprises of a clinically heterogeneous group of disorders of different aetiologies characterised by the common feature of *hyperglycemia* and its resultant short term and long term complications. The hyperglycemia in diabetes occurs due to a deficiency in insulin production or a resistance to the cellular effects of insulin. As we know, the major effects of insulin are to facilitate cellular uptake of glucose and to inhibit glycogenolysis and gluconeogenesis. All these actions of insulin result in lowering of blood glucose levels. When the deficiency of insulin is extreme, the body is unable to use glucose as a fuel, and resorts to the catabolism of fats to form ketone bodies, which leads to ketoacidosis (one of the complications of diabetes). Besides the metabolic derangement resulting from hyperglycemia and the lack of insulin action, diabetes is also associated with a set of late complications involving the eyes, kidneys and nerves and the blood vessels. It is thought that these complications are a result of uncontrolled hyperglycemia; the mechanism by which this occurs is being investigated. In the developed world, diabetes mellitus is a leading cause of blindness and a major cause of renal failure, gangrene of the extremities, and myocardial infarction.

Diagnosis of diabetes

Often diabetes mellitus presents with the classic symptoms of *polyuria, polyphagia* (increased appetite) and *polydipsia* (increased thirst), frequently coupled with weight loss. The polyuria is due to *osmotic diuresis,* since the *renal threshold* for glucose is exceeded when the blood glucose is above 180 mg/dL. Above this level, the renal tubules are unable to reabsorb any filtered glucose and the glucose is excreted in the urine. Since glucose is osmotically active it carries with it free water, which leads to polyuria and dehydration. Loss of free water, coupled with an increase in blood glucose leads to increased plasma osmolality leading to increased thirst. The inability to utilise glucose as a source of energy leads to an increased appetite, and to the breakdown of protein and fat (which manifests as weight loss).

It is common for lesser degrees of hyperglycemia to manifest with more subtle symptoms, and the patient may be diagnosed on laboratory screening for hyperglycemia. Sometimes a routine urine test reveals glucose in the urine, which implies a blood sugar above the renal threshold, and this merits further work-up to exclude diabetes mellitus.

The WHO has laid down the following *criteria for the diagnosis of diabetes mellitus* (Fig 16.26):

a. A fasting plasma glucose level >7.8 mmol/l (140 mg/dL) on at least two occasions. If a fasting level is below 6 mmol/l (108 mg/dL), diabetes mellitus is excluded.

b. When the fasting plasma glucose is between 6 and 7.8 mmol/l, a 2-hour post-meal plasma glucose becomes important. Diabetes mellitus can be diagnosed if the 2-hour sample shows a glucose level > 11.1 mmol/l (200 mg/dL). If the 2-hour sample shows a glucose value of

< 7.8 mmol/l diabetes can be excluded. If the glucose values at 2 hours is between 7.8 mmol/l and 11.1 mmol/l, *impaired glucose tolerance* (IGT) is present. Recognition of this state is important because 20 per cent of patients with IGT develop frank diabetes mellitus over a period of time.

c. In laboratories which measure whole blood glucose rather than plasma glucose, the correponding values are about 15% less than those mentioned for plasma glucose.

Some physicians favour an *oral glucose tolerance test* for the diagnosis of diabetes. This test is carried out by giving 75 grams of oral glucose, with blood sugar measurements every 30 minutes for the next two hours. Such elaborate testing is rarely needed in practice, specially since the clinical consequences of an impaired glucose tolerance on the postglucose test are unclear. If the fasting plasma glucose is between 6 and 7.8 mmol/l and a firm diagnosis of diabetes mellitus cannot be made, the patient should be put on a suitable diet, and the testing should be repeated at a later date when th diagnosis may be more clear.

Another relatively recent test more used f follow-up in a diabetic rather than for th diagnosis, is the *glycosylated hemoglobin* or th hemoglobin A_1c. This test cannot be used patients with hemoglobinopathies who hav high basal levels of hemoglobin A_1. The test based on the principle that the A_1 fraction hemoglobin gets glycosylated in patients wi chronic hyperglycemia. One of the glycosylate forms of hemoglobin A_1 is called the A fraction. Some laboratories measure only th fraction whereas others measure total levels glycosylated hemoglobin A_1. Differe laboratories have different 'normal' ranges, b levels between diabetic and non-diabet populations do not overlap. Also, because of th relatively long half-life of glycosylate hemoglobin, the levels give an indication plasma glucose levels over the previous 2- month period. This seems to be more importa than a single random glucose measurement.

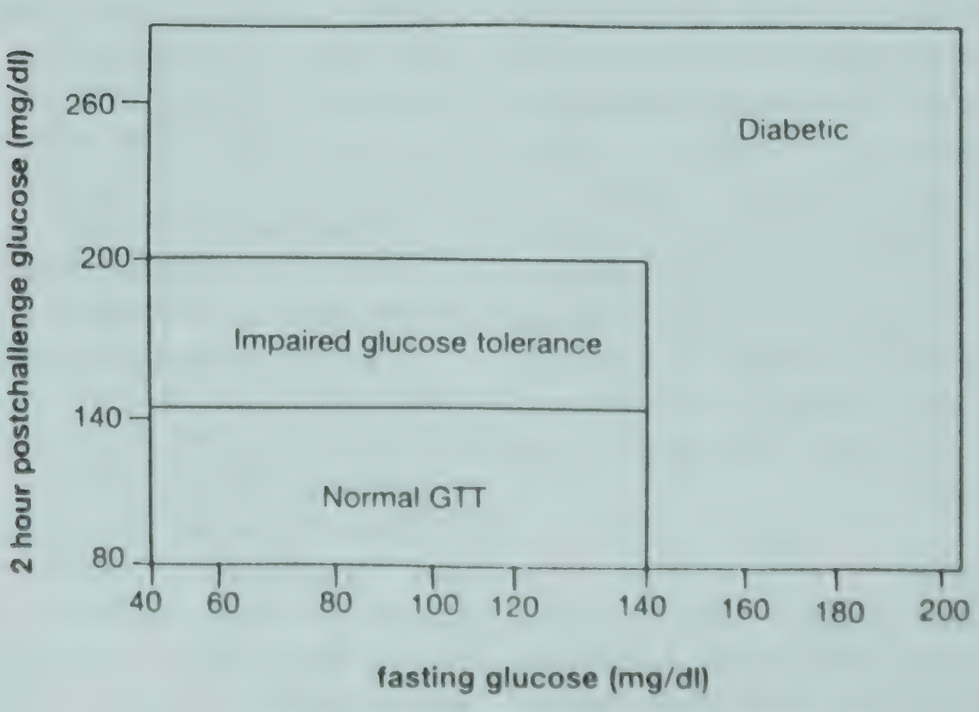


Fig 16.26 Interpretation of 75 gram oral glucose tolerance test

Physiology of glucose metabolism

Glucose is derived from three sources: by absorption from the intestine, from the breakdown of stored glycogen (*glycogenolysis*), and by synthesis from precursors, that is, lactate and amino acids (*gluconeogenesis*). For practical purposes the liver is the main organ for these processes of glycogenolysis and gluconeogenesis, though the kidney also has the enzymes required for these processes. Most organs use glucose as a fuel, but can reduce glucose utilisation in favour of β oxidation of fatty acids under conditions of glucose shortage. The brain, blood cells and renal medulla can only use glucose as a metabolic fuel. With physical activity, muscles may use large amounts of glucose, and under conditions of anerobic metabolism, lactate is produced as an end product of glycolysis. The lactate is transported to the liver for gluconeogenesis. During a fast, the muscles may mobilise amino acids by proteolysis, and alanine thus released is used for gluconeogensis by the liver thus ensuring glucose supply for organs such as the brain. Under conditions of excess glucose, glucose is used for glycogen synthesis in the liver and muscle, and for triglyceride synthesis in the adipose tissue.

In an adequately-fed person, carbohydrates form the main source of energy production. In the 'fed' state, glucose obtained from food provides most of the energy, and the excess glucose is converted to glycogen which is stored in the liver and muscle. About 6 hours after a meal, glycogen breakdown (glycogenolysis) releases glucose to provide energy until the next meal. The transport of glucose into tissues and the production of glycogen are insulin-mediated processes, whereas the breakdown of glycogen to provide glucose occurs during a low insulin state. Fat is not normally broken down to provide energy, except under conditions of prolonged fasting after glycogen has been depleted, and this takes about 24–48 hours. Triglycerides are broken down to fatty acids which are metabolised to *ketone bodies* which can be further used as fuel by the body. During prolonged fasts (of over a month) even the brain utilises ketones as a major fuel, thereby decreasing the glucose needs of the body. At this stage the main precursors for gluconeogenesis are the amino acids derived from muscle breakdown.

The main hormones regulating glucose homeostasis are insulin, glucagon, epinephrine, cortisol and growth hormone. Insulin is the main glucose lowering hormone. It causes increased cellular uptake of glucose, and acts to prevent glycogenolysis and gluconeogenesis. It also promotes formation of glycogen from glucose. Glucagon is a potent stimulator of glycogenolysis and gluconeogenesis in the liver. Epinephrine has effects similar to that of glucagon, but acts independently. Cortisol and growth hormone also stimulate glucose production, but their actions become manifest after several hours.

In addition to its effects on glucose, insulin also prevents lipolysis, whereas glucagon acts to increase fatty acid oxidation by the liver. Thus, a combination of severe insulin deficiency with normal glucagon levels, as occurs in Type 1 diabetes, favours fatty acid release and subsequent oxidation. *Ketoacids* are intermediaries in fatty acid oxidation, and they accumulate when the oxidation capacity of the liver is overwhelmed. *Ketoacidosis* is thus a complication of Type 1 diabetes, and is described later in the chapter.

Classification As mentioned at the outset, diabetes results from varying etiologies. The WHO has suggested a classification of diabetes mellitus as outlined below:

- Insulin-dependent diabetes mellitus
- Non-insulin-dependent diabetes mellitus
  - a) Non-obese
  - b) Obese
- Malnutrition-related diabetes mellitus
  - a) Protein deficient pancreatic diabetes
  - b) Fibrocalculous pancreatic diabetes
- Others
  - a) Pancreatic disease of hormonal etiology e.g. Cushing, acromegaly, glucagonoma
  - b) Drug- and chemical-induced
  - c) Abnormalities of insulin or its receptors
  - d) Certain genetic syndromes
  - e) Miscellaneous

TYPE 1 INSULIN-DEPENDENT DIABETES MELLITUS

Type 1 diabetes is also known as *autoimmune diabetes mellitus* since in these patients there is evidence of autoimmune destruction of the insulin-producing β cells in the islets of Langerhans in the pancreas. This destruction of the β cells leads to an absolute deficiency of insulin, leading to a requirement of exogenous insulin in order to maintain normoglycemia and to prevent ketosis. For this reason, Type 1 diabetes mellitus is also called Insulin-Dependent Diabetes Mellitus (IDDM). Though the destruction of β cells may be a smouldering process, the patient becomes symptomatic relatively acutely when the circulating insulin reaches a critical low level.

This disease is more common in certain genetic groups, mainly of Caucasian origin. The highest incidence is found in the Scandinavian countries. The incidence in Indians, Japanese, Chinese and Africans has been reported to be much lower. True incidence figures are not available from India, but it seems that less than 4 per cent of all diabetics in this country have true Type 1 diabetes mellitus.

The genetic influence seen in Type 1 diabetes is probably mediated through a variety of genes, many of which are still not known. However, by virtue of its being an autoimmune disease, the genes for the HLA antigens have come under close scrutiny. That the HLA subtypes are important, is borne out by the fact that HLA identity of siblings increases the risk of developing Type 1 diabetes, and that non-identity decreases the risk. The chance of a child developing diabetes if a sibling already has diabetes, is about 5–10 per cent, but this increases to about 50 per cent if the sibling with diabetes is an identical twin, since monozygotic twins have identical genes including HLA subtypes.

Various HLA alleles have been associated with an increased risk of development of diabetes and these include HLA DR3 and the HLA DQB1. It has been seen in the Caucasia population that the risk of diabetes is increase if there is no aspartate on position 57 of th protein coded by the DQB gene. The presen of aspartate at this position is protective for th development of diabetes.

Class II HLA antigens (designated by lette DR, DP or DQ) are found on lymphocyte macrophages and other specialised antige presenting cells. Class I HLA antige (designated by the letters A, B, and C) are fou on most other cells in the body. Both classes HLA proteins are on the cell surface and ser to present antigens to cells of the immu system. Certain conditions, such as vir infections, may cause excess production cytokines (such as gamma interferon), which turn cause the beta cells in the islets to expre Class II HLA antigens not normally expresse by them. In individuals with HLA Class II gen which confer susceptibility to diabete expression of these genes on the beta cell surfa may lead to their destruction by the immu cells.

Besides genetic factors, environment is al thought to play a role in the development Type 1 diabetes. This is because the disea shows seasonal and regional variation in th same country, and in genetically identical twi The disease occurs in both in only 50 per cent the cases. An association of various vir infections (including coxsackie virus, a congenital rubella) with IDDM has be observed but there is not enough evidence suggest a direct causal mechanism. It is like that an initiating factor like a virus requires t appropriate genotype (including HLA subtype to initiate an immune response to the pancrea β cells. In animal models of spontaneous a induced diabetes, it has been seen th lymphocytes from a diabetic animal can cause accelerate diabetes in a non-diabetic animal the same species. Subgroups of lymphocyt have also been identified which may prote

against such 'adoptive transfer' of diabetes from one animal to the other. Histological examination of the pancreas in humans with diabetes reveals a lymphocytic infiltation of islets which leads to selective destruction of the β cells. This process has been called *insulitis*. In animals prone to diabetes, insulitis is seen to precede the onset of hyperglycemia and the inflammation declines after the β cells are completely destroyed. In view of the ability to transfer diabetes by the transfer of lymphocytes from a diabetic animal and the early appearance of insulitis, diabetes is thought to be a disease of mainly cell-mediated immunity. However, in patients with early diabetes a variety of autoantibodies to components of islets such as anti-islet cell antibody, anti-insulin antibody, and anti-GAD (glutamic acid dehydrogenase) antibody are found. Since the humoral and cellular arms of the immune system act in close cooperation, it is likely that these antibodies are a secondary response to the initial damage of the islets. There are some workers who think that these antibodies may have a primary role, and this has been the subject of much research.

Type 1 diabetes often develops at a young age, with a peak during the adolescent years. Though it is less common after the age of 40 years, it can occur at any age. There are reports of older patients with Type 1 diabetes presenting with a smouldering onset, rather than the typically abrupt onset seen in younger patients. Initially such patients may mistakenly be diagnosed as Type 2 diabetes mellitus. Patients of Type 1 diabetes mellitus have low circulating insulin and *C peptide levels*. The C peptide is a peptide chain which is cleaved off the proinsulin molecule after it is secreted from the pancreas, and hence it is a measure of endogenous insulin production. In the early phase of the disease, patients are often asymptomatic despite the low insulin levels, until an intercurrent illness or stressful event increases insulin requirements. Since the pancreas is not able to keep up with the demand for more insulin, severe hyperglycemia supervenes. This in turn leads to osmotic diuresis and dehydration. Inability to utilise sugar due to insulin deficiency leads the body to turn to fat breakdown and ketone body formation. High levels of ketone bodies lead to acidosis and symptoms of nausea and vomiting. The patient improves after insulin therapy, and as the stressful precipitating event passes away, the patient may remain relatively healthy without therapy based on the endogenous insulin production. However, continuing destruction of the islets causes a progressive fall in insulin levels until the patient becomes symptomatic again and requires exogenous insulin. The intervening period of wellbeing after an initial acute presentation in a diabetic patient is often referred to as the *honeymoon period* (Fig 16.27).

Patients with Type 1 diabetes mellitus are often thin; an absolute deficiency of insulin leads to an inability to utilise glucose as a fuel, and thereby predisposes to protein and fat catabolism. An increased prevalence of other autoimmune diseases such as Hashimoto's thyroiditis, Addison's disease, pernicious anemia and vitiligo are seen.

TYPE 2 NON-INSULIN-DEPENDENT DIABETES MELLITUS

The underlying mechanism for Type 2 diabetes mellitus is thought to be *resistance of peripheral body tissues to the actions of insulin*, leading to a defect in glucose uptake and utilisation (Fig 16.28). All body tissues (except for the red blood cells, brain and kidneys) require insulin for glucose uptake. A resistance to insulin actions leads to hyperglycemia and associated symptoms. A loss of insulin action on the liver stimulates hepatic gluconeogenesis, which acts to further increase blood glucose levels. In an attempt to overcome the resistance to insulin, the pancreas is stimulated to release large amounts of insulin, which may act to normalise the blood glucose in the early stages. Later, the

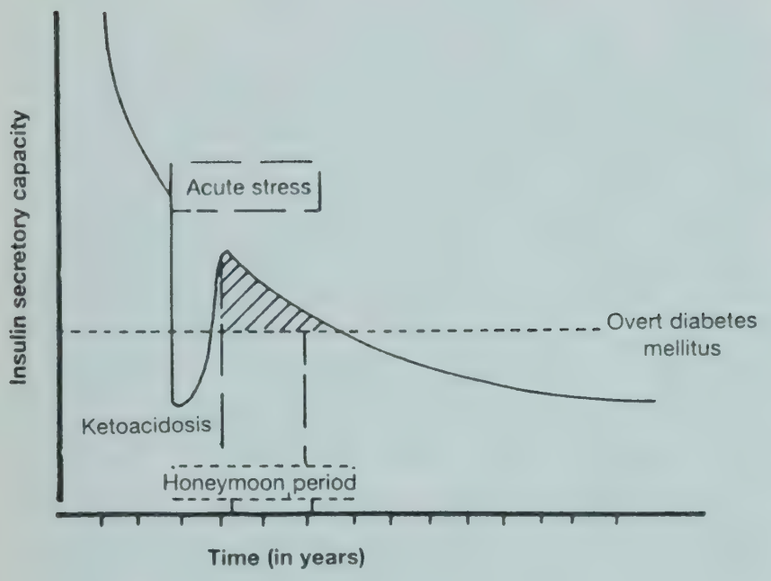


Fig 16.27 Blood glucose pattern in Type 1 diabetes mellitus

islets cannot keep up with increased insulin secretion and the person becomes hyperglycemic. It is not clear at what stage in their lives patients with Type 2 diabetes initially manifest insulin resistance, but some studies suggest that insulin resistance manifests very early in life and is compensated by the secretion of large amounts of insulin. As the person ages, the degree of resistance probably increases, the β cell function declines and the person manifests the signs of diabetes. It is interesting that hyperglycemia is itself toxic to the β cells in the pancreas, further reducing insulin secretion. In the late stages of Type 2 diabetes, the patient may have very low circulating insulin levels and she usually requires exogenous insulin. In the early stages when the β cells are capable of maintaining insulin secretion, drugs which help to increase insulin secretion and increase the sensitivity of peripheral tissues to insulin may help to maintain normoglycemia.

In any given patient a direct relation of body weight to insulin resistance is seen. This means that if a patient gains weight, the insulin resistance increases and hyperglycemia worsens. In fact in many patients diabetes become apparent after weight gain, and often a reduction in weight is all it takes to reverse the hyperglycemia. Many patients of Type 2 diabetes mellitus are obese, and a loss of weight would improve hyperglycemia. In reality weight loss is often a difficult goal to achieve. Some people have an inherent tendency to obesity, and the mechanisms for this are not fully understood and may have to do with differences in energy utilisation and loss. Non-insulin-dependent diabetes has a strong genetic predisposition, and is also linked to obesity and hypertension.

Type 2 diabetes usually has a more insidious onset than Type 1 diabetes. Often patients have a long period of asymptomatic hyperglycemia prior to the development of symptoms, and many of these patients are diagnosed on the basis of routine urine or blood glucose tests. Most patients present around or after the age of 40 years, exceptions being people with severe obesity or a strong family history of insulin resistance and Type 2 diabetes mellitus.

For some reason, patients of non-insulin-dependent diabetes mellitus do not develop the state of acute hyperglycemia with ketoacidosis. This may be related to the fact that they have some insulin action at all times to counteract glucagon; the effect of glucagon is stimulation of fatty acid oxidation and ketone production. When an untreated non-insulin dependent diabetic has severe prolonged hyperglycemia the patient gets dehydrated and the syndrome of non-ketotic hyperosmolar coma develops.

The exact prevalence of Type 2 diabetes in India is not known. However, it seems to be increasing with the increase in affluence in the population over recent years. From various reports diabetes mellitus seems to affect 5–8 per cent of the general population. Migrant Indians who have a higher standard of living seem to have a higher prevalence of diabetes, as seen in studies from the U.K. The WHO Multinational Study has also shown that migrant Indian Asians have a high rate of mortality and morbidity from

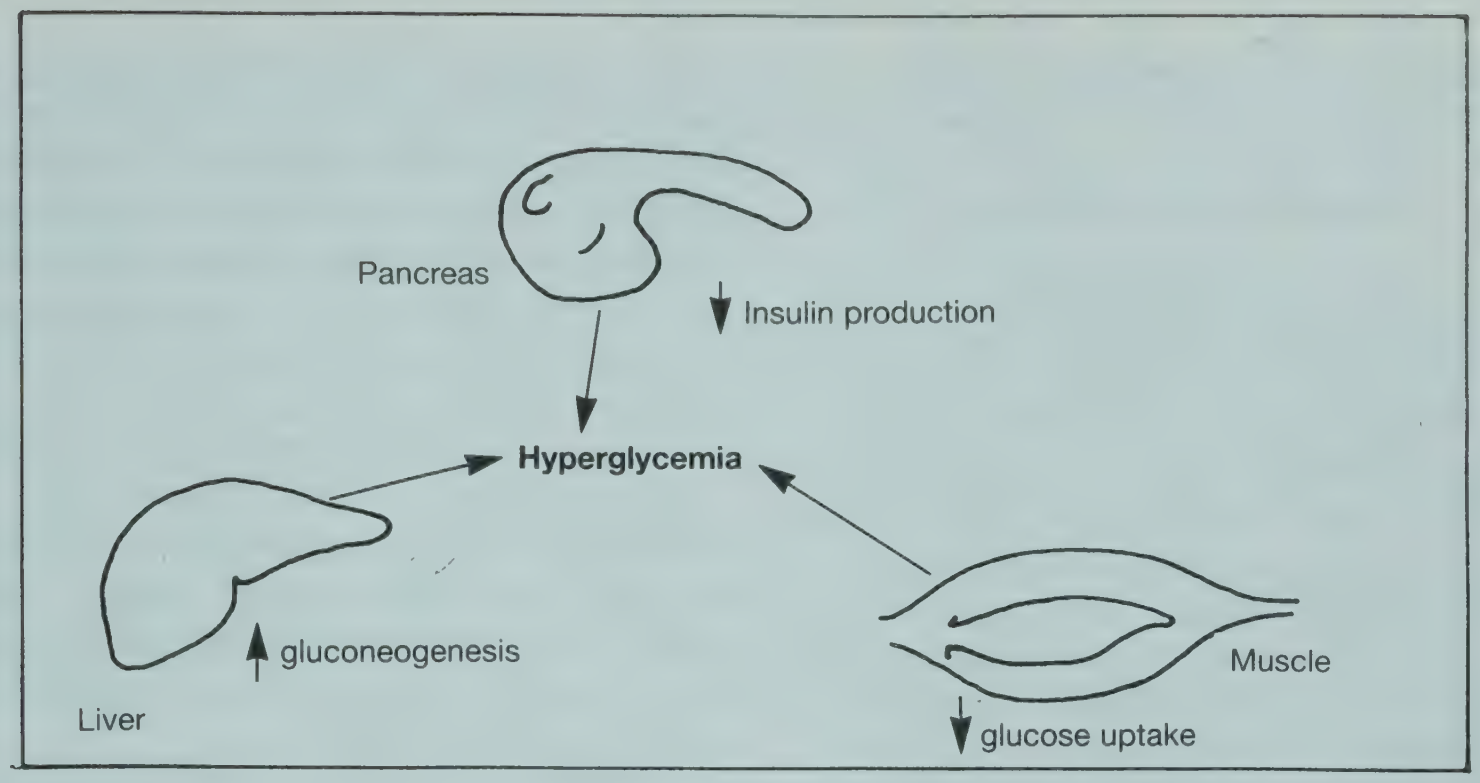


Fig 16.28 Pathogenesis of non-insulin-dependent diabetes

coronary artery disease, a part of which seems to be associated with the high prevalence of diabetes in these populations. This trend of increase in premature coronary artery disease is also being observed now in India. Studies have shown Indians to have a greater degree of insulin resistance as compared to the Caucasian population in general, and this may be the underlying basis for the metabolic abnormality leading to diabetes. In various population-based studies it has also been shown that insulin resistance is associated with dyslipidemias and this could be one of the reasons for the association of Type 2 diabetes mellitus with coronary artery disease.

MALNUTRITION-RELATED DIABETES MELLITUS

This term was proposed by a WHO study group in 1985 for a unique type of diabetes peculiar to tropical developing countries, which differed in many ways from Type 1 and Type 2 diabetes mellitus. However, due to lack of resources the sophisticated studies done on the other two varieties of diabetes have not been carried out in this subgroup of patients. Individual workers have suggested slightly different criteria but they all have a common theme. The typical patient is a young individual living in a tropical area who presents with symptoms of diabetes associated with exocrine pancreatic deficiency along with a deficiency of insulin production. These individuals are often malnourished (relative body weight <80%), and are ketosis resistant. Some of these individuals have been observed to have pancreatic calculi on plain radiographs of the abdomen and these individuals have been classified as having *fibrocalculous pancreatic diabetes* (FCPD). Individuals who are malnourished but do not have pancreatic calculi are said to have *protein deficient pancreatic diabetes mellitus (*PDPD). The resistance to ketosis is one of the major diagnostic criteria for this diagnosis and the underlying reason for this may be either preservation of residual beta cell function and/or concomitant alpha cell dysfunction. Normal alpha cell function is thought to be important in the development of ketosis as glucagon is an essential component for ketogenesis. However, the few studies done so far have not shown either beta or alpha cell function to be significantly different from a control group with classical IDDM. It has also been suggested that malnutrition-induced diabetes mellitus is associated with insulin

resistance as these patients require large amounts of insulin, but this has not been proven.

Complications of Diabetes

Besides the acute complications of diabetic ketoacidosis, and hyperosmolar non-ketotic coma which will be discussed later, chronic hyperglycemia is known to cause various long term complications which are a major cause of morbidity and mortality in the diabetic individual. Diabetes affects the eyes, nerves and the kidneys and the basis for damage to these organs is secondary to capillary damage secondary to hyperglycemia. Hence, these manifestations are described as being due to diabetic *microangiopathies*. Diabetes also accelerates the process of atherosclerosis and thereby causes *macrovascular disease* leading to coronary ischemia, and peripheral vascular disease. In addition to the vascular basis for organ damage, diabetes affects organs secondary to other processes such as non-enzymatic glycosylation of body proteins (as occurs in the skin), osmotic changes in body compartments (as occurs in acute visual changes secondary to refraction changes in the lens of the eye), and depression of leukocyte function (leading to a predisposition to infections). Most of the microvascular complications of diabetes can be prevented by good control of blood sugar, and it is presumed that the risk for macrovascular complications would also be affected favourably by control of blood glucose. Non-enzymatic glycosylation differs from the usual enzymatic glycosylation of proteins in the body in that this occurs solely on the basis of elevated blood glucose levels and is responsible for the symptoms of skin thickening and reduced joint mobility. It also forms the basis for a test for hyperglycemia that is, the glycosylated hemoglobin estimation. In patients with chronic hyperglycemia a significant proportion of their hemoglobin is glycosylated compared to non-hyperglycemic controls, and this measure gives an indication of blood sugar levels over a period of the previous 2–3 months, as turnover of th hemoglobin is slow. Glycosylation may als contribute to capillary basement membrane an glomerular basement membrane thickening see in diabetes, and to the development of cataract

It is felt that some of the complications o diabetes may be secondary to high intracellula levels of sorbitol, which is formed from glucos by the enzyme *aldose reductase*. In nerves o diabetics high sorbitol levels have bee observed, and this can potentially be reversed b a class of drugs that are aldose reductas inhibitors. Unfortunately, they have not bee shown to be of much clinical benefit in mo patients with neuropathy.

Macrovascular disease in diabetics is probab secondary to a mixture of factors including hig triglyceride levels due to insulin deficiency, hig LDL levels inherited as a concomitant genet factor with Type 2 diabetes, and insul resistance. Diabetes has also been shown to b associated with low HDL levels, which is a independent risk factor for atherosclerosis.

Eye complications

Diabetic retinopathy is a leading cause o blindness in the developed world. After 25 to 3 years of the disease, about 90 per cent of patien have retinal lesions. It starts with *backgrou retinopathy* characterised by the earliest chang of increased capillary permeability, be appreciated on a fluorescein angiogram. Later this stage areas of capillary blockage an localised dilatation occur, which progress microaneurysm formation.

Microaneurysms appear as small red dots o fundus examination. Leakage of proteins fro the hyperpermeable areas forms *hard exudate* Narrowing of capillaries leads to retinal ischem and subsequent infarction which produces th white *cotton wool exudates*. Other facto contributing to retinal ischemia in diabet include increased blood viscosity, increase platelet aggregation and increased fibrinoge levels. Patients with background retinopath also have flame-shaped superficial retin

hemorrhages, and small dot-shaped deeper retinal hemorrhages. Background retinopathy rarely affects vision unless there are exudates or hemorrhages in the macular region. Background retinopathy can progress to *proliferative retinopathy* which can seriously impair vision, and this is the reason why diabetic patients with early retinopathy should be monitored regularly for progression of retinopathy. Before frank proliferative changes in the vessels are seen, a condition called *intraretinal microvascular abnormalities* (IRMA) has frequently been described. These appear as small shunt vessels or dilatation of preexisting capillaries in the retina. Other signs of retinal ischemia such as *soft exudates* are also present at this stage, which has been termed *pre-proliferative retinopathy.*

The initiating event in proliferative retinopathy is new vessel formation, and the presumed stimulus for *neovascularisation* is retinal hypoxia secondary to previously mentioned factors. The new vessels are most prominent around the region of the optic disc. These newly formed vessels lie on the retina unsupported and are prone to rupture and bleeding into the vitreous. Such bleeding, besides impairing vision, causes the formation of fibrous tissue, which as it contracts, tends to pull on the adjacent retina to cause *traction retinal detachment.*

Proliferative retinopathy is best treated with *laser photocoagulation* which destroys new capillaries, leaky vessels and microaneurysms, and prevents further proliferation of vessels. The mechanism by which laser photocoagulation works is presumed to be destruction of the retinal tissue, which leads to reduced retinal oxygen demands, which in turn diminishes the release of factors promoting vascular proliferation. Often *pan-retinal photocoagulation* is used, and this involves producing 2000–3000 lesions over the entire retina over a 10–14 day period. *Vitrectomy* is used to remove vitreous hemorrhages and scar tissue obstructing vision.

Cataracts occur earlier in diabetics than their non-diabetic counterparts. The *snowflake cataract* showing tiny white flecks in the lens characteristically occurs in diabetics.

Neurological complications

Neuropathy in diabetes occurs in three typical forms: a *mononeuropathy* involving a cranial or peripheral nerve, a *symmetric peripheral polyneuropathy* (the most common), and *autonomic neuropathy.*

Diabetic mononeuropathy is considered to be due to disease of the vasa vasorum and is a variant of the mononeuritis multiplex seen with other vasculitic disorders. It typically involves the third, fourth or sixth cranial nerves, or the femoral, sciatic, median or ulnar nerve. The typical clinical presentation is the sudden onset of wrist drop, foot drop, or a paralysis of extra-ocular eye movement typical for the cranial nerve involved. When the third nerve is involved, the pupillary fibres are generally spared since these run on the outside of the nerve and are less susceptible to ischemia. The mononeuropathy subsides spontaneously in days to a few weeks. *Diabetic amyotrophy* is a condition characterised by wasting, weakness and fasciculations in muscles of the limb girdle distribution. It also occurs secondary to vascular involvement of the nerves supplying these muscles.

The most common manifestation of diabetic peripheral neuropathy is symmetric loss of sensation in the distal lower extremities. The deep tendon reflex at the ankle is frequently absent. A common symptom is deep burning pain worse at night, and numbness and tingling of the extremity. The pain gets better as the neurons are completely destroyed, but the danger of unnoticed foot injury increases, and diabetics with neuropathy should take extra care to avoid this. Loss of sensation from joints leads to a destructive arthropathy known as *Charcot's joint* more common in the ankle joints in patients with diabetes.

The manifestations of autonomic neuropathy include impotence, orthostatic hypotension, motility disturbances of the bladder and bowel and anhidrosis. *Diabetic gastroenteropathy* may be troublesome, and *gastroparesis* leads to delayed gastric emptying and a feeling of fullness. Diabetics are more prone to both chronic constipation and troublesome diarrhea, due to impaired bowel motility. Bacterial overgrowth in the intestine is a contributing factor for the latter.

There is little in the way of treatment for diabetic neuropathy, and most treatment is symptomatic. Amitriptyline, carbamazepine and phenytoin may help in controlling painful neuropathy, besides topical medications such as capsaicin.

Renal complications

Diabetes is a major cause of chronic renal failure. The occurrence of nephropathy seems to be a function of the duration of diabetes. Histologically, the lesions of nephropathy occur in the renal glomerulus and involve thickening of the glomerular basement membrane, increase in mesangial matrix, and subintimal thickening of efferent and afferent glomerular arterioles. These changes are also thought to be secondary to increased capillary permeability and leakage of proteins into the glomeruli. The thickening of the mesangial matrix can be nodular, and when these nodules occur at the periphery of the glomerular tufts, they are large and spherical and are described as the *Kimmelstiel-Wilson lesion*. These nodules, and the thickening of the efferent arterioles may be the earliest changes seen in diabetes after five years of onset.

In diabetes mellitus, the glomerular filtration rate is high, with higher intraglomerular capillary pressures as compared to healthy controls. This coupled with increased capillary permeability leads to proteinuria in the diabetic. In early stages, the protein loss is small and this is known as *microalbuminuria* (<300 mg/24 hours), since it cannot be measured by urinary 'dipstick'. Microproteinuria suggests a high risk of development of future *macroproteinuria* (>300 mg/day), though it must be emphasised that the presence and level of microproteinuria is not a constant feature in any given patient and may be affected by exercise, and glucose control. The development of macroproteinuria signifies the beginning of slowly progressive renal dysfunction with declining glomerular filtration rates. At this stage retinopathy is almost always present.

The mechanism for *hyperperfusion* in early diabetic nephropathy is not entirely clear, but it has been suggested that prevention of hyperperfusion, to enable intraglomerular pressures to return towards normal, prevents the progression of diabetic nephropathy. The reason for basement membrane thickening is also unknown. Diabetics also seem to develop the condition of *hyporeninemic hypoaldosteronism*, in that they lose the ability of the juxtaglomerular apparatus to secrete renin in response to the usual stimuli of hypotension and hyponatremia. The loss of renin production leads to decreased aldosterone production, which manifests as hyperkalemia and hyperchloremic acidosis.

Besides glomerular disease, diabetics are prone to urinary tract infections, and *renal papillary necrosis*. The latter condition manifests as flank pain and hematuria and there are leukocytes in the urine.

There is no curative treatment for diabetic nephropathy, though glycemic control helps in delaying the progression of the disease and slowing the progression of microproteinuria to frank proteinuria. Angiotensin converting enzyme inhibitors appear to delay the progression of renal disease presumably by reducing intraglomerular pressures. The one factor which markedly accelerates the progression of glomerular disease is hypertension, and this should be treated vigorously in the diabetic patient. Guidelines for management of hypertension in a diabetic suggest a lower threshold for starting treatment than in the general population.

Once a patient progresses to frank renal failure, dialysis may have to be instituted. Renal transplantation was previously contraindicated in the diabetic patient because the transplanted kidney is at a risk for development of nephropathy; as resources and availability of donor organs improve more diabetics are agreeing to undergo renal transplants in the developed countries. This goal is made easier if the transplant of cadaveric organs is permissible by law.

The diabetic foot

Diabetic patients are more prone to foot infections than the normal population. This is due to a combination of factors. Peripheral vascular disease leads to ischemia of the feet (which slows wound healing), and neuropathy makes these people more prone to unnoticed foot injuries. Hyperglycemia is also thought to play a permissive role in the development of foot infections, mainly by its inhibitory action on leukocytes. Any foot infection in a diabetic has the potential to spread, and the presence of severe peripheral vascular disease is a poor prognostic factor in such a patient. Early foot infections are treated with *appropriate antibiotics* and *local measures*. Spread of the infection to underlying bone may be missed due to the absence of pain in the presence of neuropathy.

In patients with poorly healing foot wounds *revascularisation* of the lower limbs may be considered if it is surgically feasible. In severe infections which are spreading, *amputation* of the limb may have to be resorted to as a last resort. Care has to be taken to ensure that the level chosen has good blood supply to allow for adequate healing after surgery. An attempt to prevent foot injuries in the diabetic is very important. This is achieved by wearing wide comfortable shoes, avoiding putting feet in hot water, keeping feet clean and inspecting them daily for minor injuries, and maintaining good nail hygiene. If available, help from a podiatrist may be useful.

Cardiovascular complications

In addition to peripheral vascular disease, arteriosclerotic coronary artery and cerebrovascular disease are common in diabetic patients. Besides angina and frank myocardial infarction, silent myocardial ischemia is more common in the diabetic. *Diabetic cardiomyopathy* occurs when there is cardiac dilatation with evidence of left ventricular dysfunction, in the absence of any identifiable coronary vascular narrowing. This may be related to small coronary vessel disease in the heart which is not visible on coronary angiography.

TREATMENT OF DIABETES MELLITUS

The aim of treatment in diabetes mellitus, regardless of etiology, is to achieve normoglycemia. This involves avoidance of both hyperglycemia and hypoglycemia. The latter is often the result of therapy in a diabetic patient. Since diabetes is a chronic disease, it is absolutely essential that patients be educated about the nature and management of their disease. Patient education and motivation requires time and resources, and lack of patient education is the main drawback in the effective treatment of diabetics today.

In a diabetic patient, the three most important factors involved in the regulation of blood glucose levels are diet, exercise and insulin or an oral hypoglycemic agent.

Diet

Understanding the relationship of blood glucose to food intake is important in the management of diabetes mellitus. Oral intake of carbohydrates increases blood sugar levels. *Simple* carbohydrates such as sucrose (cane sugar), are rapidly and efficiently absorbed and cause an acute increase in blood glucose. To maintain normoglycemia after a diet rich in simple carbohydrates, the pancreas must secrete a large amount of insulin over a short period, which is not possible in a diabetic patient, especially if the person is maintained on exogenous insulin.

Complex carbohydrates on the other hand require digestive processes to be broken down before absorption, and cause a gradual yet sustained change in blood sugar which is better for a person on fixed doses of insulin. However, whatever the composition of carbohydrates in a diet, the blood glucose is always higher after a meal than before it. Therefore, to achieve good control of blood glucose, insulin injections should be timed in such a way that the peak rise in blood glucose and peak insulin action coincide. It is important to understand the pharmacokinetics of the different insulin preparations and this is discussed later in the section on insulin use.

It is recommended that the diabetic patient consume a diet which consists of 50–60 per cent complex carbohydrates, with 25–35 per cent fats (most of which should be unsaturated fats). This amount of fat is required to provide the essential fatty acids and to maintain adequate body fat stores. About 15 per cent of the calories should come from proteins. The total number of calories consumed should be proportional to the amount of activity, and would typically be about 40 calories/kg/day for an active 18-year old and about 30 calories/kg/day for a relatively sedentary 60-year old. An obese diabetic should get about 10 per cent less than his daily caloric requirements to help him lose weight. The calories should be distributed evenly through the main meals with proportionately smaller amounts allocated to any snacks. Eating habits vary with cultural, regional and individual preferences, and every attempt must be made to individualise a meal plan. Caloric contents of various foods are available from books and pamphlets on the subject. Since the carbohydrate component of the meal is responsible for the increase in the postmeal glucose, many patients find the concept of *carbohydrate exchanges* helpful. Carbohydrate exchanges are a simple way of comparing the carbohydrate content of various foods, thereby giving the patient equivalent amounts of these foods as far as carbohydrates are concerned. The help of a qualified dietician is invaluable in the management of a diabetic patient.

Exercise

Exercise acts to increase glucose uptake by the muscles, both by improving circulation through the muscles, and by increasing insulin-mediated glucose uptake. This leads to lower blood glucose levels for the same degree of 'insulinisation'. There is evidence that in the patient with NIDDM exercise reduces insulin resistance, independent of its effect of causing weight loss. Thus, regular exercise is beneficial in diabetics.

It should also be borne in mind that irregular or unaccustomed exercise in a patient who is controlled on a steady dose of insulin may lead to hypoglycemia. This can occur upto 12–18 hours after the exercise. Therefore, appropriate reduction of hypoglycemic medications, or an increase in caloric intake should accompany any strenuous exercise which is not routine.

Insulin

All patients of IDDM and many patients of NIDDM require insulin to maintain glycemic control. Insulin lowers blood sugars, but as insulin has to be given in intermittent injections, it is difficult to maintain smooth control of blood sugar throughout the day. In non-diabetics the blood glucose is maintained within a narrow range as the pancreas constantly senses the level of glucose and secretes the required amount of insulin. The ideal treatment for a diabetic patient would therefore be an *artificial pancreas* which could constantly sense glucose and inject the required amounts of insulin. However the closest we are to this is the insulin pump, a small portable device which constantly injects insulin at a preset rate which can be varied with the time of the day. In addition, the patient can inject small boluses of insulin before meals through the pump. However, use of the pumps requires motivation as the patient has to monitor blood glucose frequently to make the necessary

djustments. In addition, pumps are expensive, nd not available to all patients.

The commonest method of insulin dministration is intermittent subcutaneous njections of insulin. Multiple daily doses of nsulin achieve smoother control of blood lucose than one or two daily injections, and nost insulin-dependent diabetics should be on a nultiple daily dose regimen. Generally, a nixture of the short-acting regular insulin and an ntermediate-acting insulin (such as NPH insulin r lente insulin) are used. For the night-time nsulin dose some physicians prefer to prescribe long-acting insulin (such as ultralente insulin). The pharmacokinetics of the different insulin preparations vary with individual patients, and are also different for insulin obtained from different animal species. The various preparations of human insulin seem to peak earlier and have a somewhat shorter duration of action than their porcine and bovine counterparts. A rough estimate of the time of peak action and the duration of action of the various preparations of pork insulin are given in Table 16.18. In the past, insulin was extracted from the pancreas of pigs and cows, but nowadays the the most efficient way to produce insulin is by recombinant DNA technology using the *E.coli* bacillus to produce human insulin.

The different insulin types may be mixed in the syringe prior to injection, and the pharmacokinetics of the two insulins will be roughly the same as if they were administered separately. It is recommended that regular insulin not be mixed with lente insulin. Taking regular insulin with an intermediate type of insulin at the same time has the advantage of providing an early peak action coupled with prolonged insulin effect. Since regular insulin starts to act about half an hour after administration, it is recommended it be taken 30 minutes before a meal so that its action coincides with the rise in glucose which would occur after the meal. If the morning dose of regular insulin has some NPH insulin mixed with it, the combination would cover the afternoon meal taken 4–6 hours after breakfast. A similar mixture of regular and NPH insulin could be taken before the evening meal, though hypoglycemia should be watched out for when the NPH insulin peaks about 6–8 hours later. If this occurs, a bedtime snack should be taken, or the dose of NPH insulin reduced. Alternatively, bedtime ultralente insulin could be substituted for the evening NPH since this has a longer duration of action and a smaller peak. (Fig 16.29).

The early morning period is often marked by hyperglycemia, and this is thought to be due to the high levels of cortisol and growth hormones at this time since both these hormones act to raise blood glucose levels. This phenomenon is known as the *dawn phenomenon*, and it requires an increase in the previous night's long or intermediate-acting insulin. Alternatively the evening dose of insulin can be split so that the regular insulin can be taken before dinner, while the intermediate-acting insulin is taken at bedtime. Sometimes hyperglycemia in the morning may be due to a *rebound phenomenon*

Table 16.18 Pharmacokinetics of insulin preparations

Type of insulin	*Onset of action (hours)*	*Peak of action (hours)*	*Duration of action (hours)*
Regular insulin	0.5–2	3–4	6–8
NPH insulin	4–6	8–14	18–26
Lente insulin	4–6	8–14	18–24
Ultralente insulin	8–14	8–20	24–28

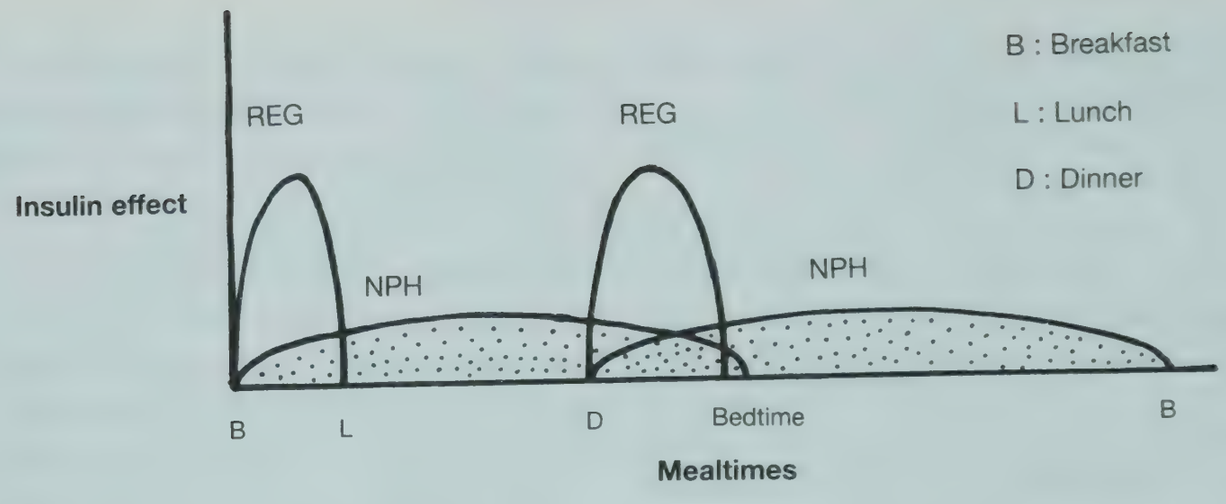


Fig 16.29 Insulin effect of a regimen with two insulin injections a day, of short (regular) and intermediate acting (NPH) insulin

from hypoglycemia in the middle of the night. This is because hypoglycemia triggers the release of epinephrine, glucagon and cortisol to increase the blood sugar levels. If this occur, it can be confirmed by finding a low blood sugar at around 3 a.m. when the night dose of intermediate-acting insulin has its peak effect. The solution in this case would be to reduce the evening dose of intermediate-acting insulin. Once the kinetics of insulin in a particular patient are known, therapy has to be individualised to minimise wide fluctuations in blood glucose, and this is done both by varying the type, amount and the timing of the insulin. Sometimes it may be helpful for the patient to change her eating habits. As a general guideline about two-thirds of the total daily dose of insulin should be given in the morning, while the rest is given in the evening. Also, two-thirds of any dose should comprise of intermediate-or long-acting insulin, and a third as regular insulin. Generally, patients require 12–20 units per day initially, but requirements vary depending on the degree of resistance to insulin and the presence or absence of antibodies to exogenous insulin. For Type 1 diabetics who make little or no insulin, typically more insulin injections are required in the day for smooth blood sugar control. In Type 2 diabetics often good control is possible with one or two injections of insulin, and if control is poor, increasing the number of injections may not actually improve the glucose levels. For the convenience of patients, man fixed ratio combinations of regular an intermediate-acting insulins is available, th most popular being a preparation with 30 pe cent regular and 70 per cent NPH insulin.

For good blood glucose control it is importan that the pattern of insulin administration mim insulin secretion by the pancreas in norma individuals. However, since regular insulin take half an hour after injection for onset of actio and peaks in 2–3 hours, an injection taken ju prior to meals has its main effect lagging behin the rise in blood glucose which occu postprandially. In an effort to produce an insuli that acts rapidly and for a short perio researchers have discovered an insulin analogu in which the two amino acids lysine and prolin in the insulin molecule are switched in positio giving it these characteristics. This analogue known as *Lys-Pro Insulin* and will be soon b available commercially.

The patient can usually take insulin in variou sites including the abdomen, thigh and arm However, the absorption from various site varies, and may also vary from day to day an this is a factor to be considered in any patie with erratic blood sugar control. It is sour clinical practice to instruct the patient to take th insulin injection at a particular site at a particul time of the day, that is, the thigh before breakfa and the abdomen before dinner.

For good blood glucose control on any insulin regimen it is essential that the patient be able to monitor blood glucose regularly, so that appropriate changes in insulin dosage can be made. For this it is preferable that the patient have a home blood glucose monitor. These are reasonably priced, but may still be out of reach of most diabetics in our country. In the absence of ability to monitor blood glucose, intensive control of blood glucose may be dangerous as there is a real risk of hypoglycemia. In patients who are unable to monitor blood glucose at home monitoring adjustments in insulin dose are based on occasional laboratory blood glucose values obtained at different times of the day, along with urine sugar tests. The urine should be tested by a *double voiding technique,* to make sure the sample tested reflects current blood sugar levels. Based on blood sugar or urine levels, adjustments in insulin are so made that the effect of the insulin dose adjustment is maximum at the time of the day when the blood glucose level is out of the desired range. For example, a person with pre-lunch hyperglycemia, and good control at dinnertime, may benefit from increasing his pre-breakfast dose of regular insulin. If the same person had high glucose levels, both pre-lunch and pre-dinner, an increase in the morning NPH may help. Adjustments should be conservative, and change should be made in one component at a time. It is suggested that the change in insulin dose be a maximum of 10 per cent of previous doses.

In hot climates insulin must be stored in the refrigerator. Limited reuse of insulin syringes, for financial reasons, has been shown to be safe provided the syringes are kept hygienically. The major adverse effect of insulin is hypoglycemia, and all patients must be taught how to recognise the symptoms, and treat it. The treatment consists of a carbohydrate snack, and if the symptoms are severe the patient may self-administer 1 mg of glucagon intramuscularly. Symptoms of altered sensorium mandate immediate transfer to a hospital for intravenous glucose administration and for observation. It is recommended that all patients on insulin wear a bracelet identifying them as diabetics. Other side effects of insulin include *insulin allergy,* and insulin *lipoatrophy* or *lipohypertrophy* which are localised areas of fat loss or hypertrophy at insulin injection sites, respectively.

Oral hypoglycemic agents There are two classes of hypoglycemic agents in use currently. They are the *sulphonylureas* and the *biguanides.* These drugs differ in their mechanism of action. Both of them require endogenous insulin production in order to have an effect, and therefore can only be used in patients with NIDDM. Even in these individuals, there are some who respond initially to these drugs but eventually require insulin. The pregnant patient with gestational diabetes should always be on insulin since tight control of glucose during pregnancy is important to avoid complications, and there are also concerns about the potential teratogenic effects of oral hypoglycemic agents. The ideal patient for oral hypoglycemic drug therapy is the overweight NIDDM patient who has not responded to a regimen of diet and exercise. Though many of these patients may have less than an ideal response to oral hypoglycemic agents, insulin therapy is not the solution in these patients; insulin promotes appetite, and reduces fat catabolism thereby promoting weight gain; in addition, there may be insulin resistance in these patients. Therefore, the treatment of NIDDM patients is sometimes difficult and the best regimen has to be individualised. Combination of drugs and insulin may be used if either agent does not provide good results.

The overall failure rate of oral hypoglycemic agents is 10 per cent per year. Causes of failure to respond to an oral agent include

a. true failure (insulinopenia);
b. incorrect diagnosis; the patient may have diabetes of autoimmune origin;
c. the concomitant use of drugs such as steroids which aggravate hyperglycemia;

d. rarely, the development of an underlying pancreatic malignancy.

Sulphonylureas act by increasing insulin release from the pancreas, and to a lesser extent by increasing glucose uptake by peripheral tissues. There are various drugs available in this class. Tolbutamide, one of the oldest drugs has a short half-life, and is metabolised by the liver to inactive metabolites. Hence, it is the preferred drug in patients with renal failure. Chlorpropamide, on the other hand, has a long half-life of 36–72 hours, and is excreted unchanged by the kidneys. Newer drugs of the sulphonylurea group include glyburide, glipizide, and acetohexamide. All these drugs have an intermediate duration of action of 18–24 hours and can be given once or twice a day. They are metabolised to other active intermediates in the liver. A list of these drugs is given in Table 16.19.

The biguanides include metformin and phenformin. Their mechanism of action is mainly by reducing hepatic gluconeogenesis. They also act by reducing intestinal absorption of glucose, and by increasing glucose uptake by peripheral tissues. Since they do not increase insulin release from the pancreas, they do not cause hypoglycemia in normoglycemic individuals. Metformin is more widely used around the world, as Phenformin is more likely to cause *lactic acidosis,* the most severe adverse effect of this group of drugs. Since these drugs are excreted unchanged by the kidneys, they should not be given in renal failure. Also, since lactates are metabolised by the liver, they should not be given in liver disease. Other adverse effects of these drugs include anorexia, and rarely, a skin rash. A combination of Metformin with a sulphonylurea is used to delay or avoid treatment with insulin when either oral agent has failed.

Newer oral agents include *acarbose,* an intestinal disaccharidase inhibitor, which delays the absorption of the disaccharide like sucrose and maltose and other starches, thereby blunting the postprandial glucose rise. Acarbose lowers blood glucose only modestly in Type 2 diabetics and has a role in conjunction with other agents. *Thiazolidinedione derivatives* (Proglitazone) are agents that sensitise the liver and other peripheral tissues to the action of insulin at the receptor and postreceptor levels and may have a role in the treatment of Type 2 diabetes in the future.

Initiating therapy and follow-up

The initial treatment depends on two main factors: a) the type of diabetes, i.e., Type 1 or Type 2, and b) the presence of other factors such as obesity, the degree of hyperglycemia, and acute intercurrent illness at the time of diagnosis.

All patients with Type 1 diabetes mellitus should be started on insulin at the time of diagnosis along with appropriate advice regarding diet and exercise. This is because such patients have an absolute deficiency of insulin

Table 16.19 Oral hypoglycemic agents

Generic name	*Daily dose*	*Approximate biological half-life*
Tolbutamide	500–3000 mg	4 hours
Chlorpropamide	100–750 mg	36–72 hours
Glibenclamide	1.25–15 mg	24 hours
Glyburide	1.25–20 mg	24 hours
Glipizide	5–40 mg	24 hours
Metformin	500–2500 mg	2–5 hours

and drugs do little to enhance insulin production in them. People with an absolute deficiency of insulin are prone to uncontrolled ketoacidosis in the absence of exogenous insulin, and hence these patients should always have some insulin cover throughout the day. Sometimes when such patients cannot tolerate food orally (due to conditions causing nausea and vomiting), they may have to be admitted to a hospital for intravenous glucose infusions, so that some degree of insulinisation can be maintained without the occurrence of hypoglycemia. Generally, with most illnesses insulin requirements are seen to rise in most diabetics, and this is due to a state of insulin resistance induced by illness.

Patients of Type 1 diabetes mellitus require a minimum of two to three insulin injections a day, with most injections comprising a mixture of a short and an intermediate-or long-acting insulin. It is not possible to maintain smooth control of blood sugar in such patients with a single injection or with even two injections of an intermediate-acting insulin. Initially after diagnosis in these patients, 16–20 units of insulin/day in divided doses may be adequate. Changes should be made gradually and one component of the insulin regimen should be changed at a time, so that further changes can proceed in a logical manner. It should be kept in mind that these patients often have a 'honeymoon period' and insulin requirements may initially decrease before increasing again. Though severe hypoglycemia should be avoided at all costs, most well-controlled patients have mild hypoglycemic symptoms one to two times a week and these can easily be treated with a snack. Hypoglycemia occurring with a constant pattern requires reduction in that insulin dose which is predicted to have a maximal effect at that time of the day. To make adjustments in insulin, it is highly desirable that patients should be able to monitor their own blood sugars several times a day. Recommended times for monitoring blood glucose may be before meals and at bedtime. Patients can adjust their short-acting insulin before meals themselves, if they are going to eat a larger than usual meal or a small meal, or if intensive bursts of physical activity are expected. Intermediate-acting insulin can be reduced if they anticipate a prolonged period of increased activity such as playing a football game. Most motivated patients are able to make these adjustments on the basis of previous experience.

Patients with Type 2 diabetes mellitus *who are not overweight* may be controlled on regular exercise and a normal caloric diet which avoids simple carbohydrates. Most such people need oral hypoglycemics in addition, but often fail to achieve blood sugar control after varying periods of time and may then require insulin. Such patients can be started on a single morning dose of intermediate-acting insulin, since most caloric intake occurs during the day, but they may require additional injections depending on the blood glucose control. Type 2 diabetics who do not respond adequately to oral hypoglycemics typically require 12–16 units of an intermediate-acting insulin per day initially. They often require much larger insulin doses later and these have to be split into two daily doses. Often better control is obtained with a split dose of a premixed insulin (that is, 70% NPH to 30% regular). More complicated regimens in these patients may not produce better results than the ones mentioned above.

In the *obese* Type 2 diabetic, the role of dietary restriction both in terms of composition (that is, avoidance of simple carbohydrates, and saturated fat) and total caloric intake are the most important part of therapy. The desired caloric intake can be calculated with the help of a dietician, and depends on the ideal body weight and degree of physical activity. Dietary restriction coupled with exercise is capable of reducing blood glucose and weight in the majority of such people. However, weight reduction is often difficult to sustain, and until the pathogenesis of obesity is better understood more specific therapy may not be available.

Therefore, if diet and exercise fail, therapy with oral hypoglycemic agents may be initiated. Metformin may be useful as its effect as an anorectic agent may promote weight loss and improve glucose tolerance. Most of the patients however, have poor control even on oral hypoglycemics and are often given insulin. The main drawback of insulin is that many of these patients gain weight while on insulin and even on conclusion of therapy, show a blood glucose in the range that was seen at the time of starting therapy. Weight gain should be carefully monitored while these patients are on insulin therapy.

All patients with diabetes mellitus should be followed up on a regular basis to assess the adequacy of blood sugar control, and to detect the development of any complications. The adequacy of control over the previous 2–3 months can be assessed with measurement of the glycosylated hemoglobin fraction. An eye examination (to assess for retinopathy) should be taken on an annual basis starting five years from diagnosis in a Type 1 diabetic and regularly from the time of diagnosis in a Type 2 diabetic. This is because patients with Type 2 diabetes often have undetected hyperglycemia for prolonged periods prior to diagnosis. Similarly, urine should be monitored for the development of albuminuria. If albuminuria is present renal function should be assessed in greater detail (such as measurement of the creatinine clearance). There is some evidence that therapy with ACE inhibitors may delay the evolution of overt renal failure from the stage of proteinuria. Hypertension should be treated aggressively since its presence has been shown to accelerate the rate of renal dysfunction. Thyroid functions may be monitored periodically in the Type 1 diabetics if feasible, since they have a higher incidence of autoimmune thyroid disease. Peripheral pulses should be carefully palpated to assess the adequacy of circulation. Peripheral vascular disease can also be assessed by other signs such as loss of hair over the distal legs and toes, and dystrophic changes in the nails. Serum lipids should be monitored since diabetics have a higher incidence of dyslipidemias as compared to the general population. At the time of diagnosis Type 1 diabetics often have high triglyceride levels which are frequently corrected by insulin therapy. Type 2 diabetics often have a low HDL cholesterol fraction with elevated LDL levels. These lipid abnormalities are not corrected by insulin therapy and have to be treated independently.

SPECIAL SITUATIONS IN DIABETES MELLITUS

Diabetes in pregnancy (see also Chapter 20)

Pregnancy in a diabetic woman poses certain problems for both the fetus and the patient. It has been demonstrated that elevated levels of blood glucose are associated with increased perinatal mortality and specific congenital malformations in the fetus. There is also a tendency for increased fetal growth, which is known as *macrosomia*. This occurs because the fetal pancreas produces excess amounts of insulin (which is a growth promoting hormone) to compensate for the hyperglycemia (which results from the transfer of glucose from the maternal circulation).

Pregnancy and diabetes may be associated in two ways. A patient with preexisting Type 1 or Type 2 diabetes may become pregnant. Alternatively females who are normally non-diabetic, may develop impaired glucose tolerance or even frank diabetes during pregnancy, known as *gestational diabetes*. This is because pregnancy is known to be associated with a decrease in sensitivity to insulin leading to a higher requirement of insulin to maintain euglycemia. Patients who cannot increase insulin secretion manifest diabetes during pregnancy. With the return of insulin sensitivity most of these patients normalise after pregnancy though some may become diabetic again in later years.

In patients of Type 1 diabetes mellitus the glucose control with previous doses of insulin may not be adequate due to altered dietary intake and metabolism during pregnancy. The patient's diet should be adjusted to allow for adequate weight gain during pregnancy. Insulin should be adjusted for tighter blood glucose control with closer monitoring.

It is widely recommended that all pregnant females be screened at 24–28 weeks of gestation for diabetes, because this is when insulin resistance is at a high level. Some authorities recommend an oral glucose tolerance test for screening purposes. The goal of management is to prevent perinatal mortality and morbidity. For good control of blood glucose it is essential that glucose is monitored frequently preferably using home blood glucose meters. Dietary modifications are important in patients with gestational diabetes. Caloric reduction may be prescribed in frankly obese patients. Enough caloric intake should be maintained in the non-obese patients to allow for the normal weight gain of 10–12 kg during the pregnancy. Starvation (as measured by the presence of ketones in the urine of these patients) should be avoided. In all patients of gestational diabetes who are not normoglycemic on dietary management, insulin therapy is prescribed. Oral hypoglycemics are avoided in view of their potential teratogenic effects. Moreover insulin affords tighter control, and the aim of therapy is to maintain glucose in the normal range. Often more than one insulin injection in a day may be required. Similar recommendations apply to the treatment of the preexisting Type 2 diabetes mellitus patient who becomes pregnant.

Diabetes and surgery

Surgery in a diabetic patient is a special situation. Often the patient cannot eat for as long as a day due to the effects of general anesthesia; this requires a change in the insulin regime. Also, surgery is a period of stress and is associated with a rise in cortisol and catecholamines, both of which cause a hyperglycemic response.

All patients who are going to be fasting for a period of time prior to the surgical procedure should be maintained on a 5 per cent dextrose infusion before the surgery. The usual dose of intermediate acting insulin (i.e., NPH or lente) is either omitted or halved on the morning of the surgery, and the plasma glucose is maintained between 150–200 mg/dL during surgery by adjusting the dextrose infusion. Intermittent doses of subcutaneous regular insulin are given as required until the patient starts eating again and can be given the usual dose of insulin. In a Type 2 diabetic who is taking an oral hypoglycemic agent, the oral hypoglcemic agent is often omitted and the patient is controlled with regular insulin during surgery.

Diabetic Comas

Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) is a metabolic derangement consisting of three concurrent abnormalities: hyperglycemia, high levels of ketone bodies and metabolic acidosis. This state occurs due to an absolute insulin deficiency associated with an unopposed effect of glucagon on glucose and lipid metabolism. This combination leads to breakdown of fatty acids to ketone bodies and stimulation of gluconeogenesis. Ketone bodies (that is, acetoacetate and hydroxybutyrate) are dissociated at physiologic pH to H^+ and the ketoanion and this leads to acidosis by depleting both intracellular and extracellular buffers. The acidosis is reflected by a decreased serum pH. The depletion of bicarbonate and retention of the ketoanions in the plasma leads to an increased anion gap metabolic acidosis. It may be recalled that the anion gap is calculated as :

$$\text{Anion Gap} = \text{Serum } Na^+ - (\text{Serum } HCO_3^- + \text{Serum } Cl^-)$$

The anion gap is normally 8–16 mmol/L. Since the concentration of anions and cations is always equal in serum, the above formula gives us an

indication of the concentration of anions other than bicarbonate and chloride– the 'unmeasured anions'. Sodium is the only major cation (since the concentration of potassium is small it is ignored in the above forumla). Besides the measured anions (that is, bicarbonate and chloride), the negative charge on albumin and, to a lesser extent phosphate and sulphate make up the normal anion gap of 8–16 mmol/L. However, when there is accumulation of other organic acids such as ketoacids, lactic acid, salicylates, and other anions (such as in poisoning and renal failure) the anion gap is increased. The measurement of the anion gap, and if indicated, specific tests to identify the excessive anion may help in the diagnosis of a patient who presents with metabolic acidosis. The common precipitating events for DKA are infections, non-compliance with treatment, and newly-diagnosed diabetes. In a quarter of the cases no precipitating event can be identified.

The patient with DKA is dehydrated from the osmotic diuresis (due to hyperglycemia), coupled with fluid losses from vomiting (which occurs secondary to the high ketone levels).

The osmotic diuresis leads to sodium and potassium losses in the urine. Since acidosis is associated with movement of potassium from the intracellular to extracellular compartment, the serum potassium may be normal at the time of presentation despite severe depletion of the intracellular potassium. As the acidosis and dehydration are corrected with therapy, the potassium deficit becomes apparent and should be monitored. Moreover, insulin acts to drive potassium into the cells and contributes to the hypokalemia seen during treatment of DKA.

Besides dehydration, clinical signs of severe acidosis may be apparent, such as the typical sighing respiration called *Kussmaul's breathing*. When acidosis and electrolyte disturbances are more marked, there is alteration of consciousness leading to a state of coma.

Laboratory investigations reveal hyperglycemia, which is generally severe, though acidosis and ketonemia can occur with blood glucose levels in the 200–300 mg/dl range. The arterial blood pH is <7.3, and plasma bicarbonate is <15 mmol/L. Plasma osmolality is increased. As mentioned above, the anion gap is high and the ketone bodies (acetoacetate and β-hydroxybutyrate) are increased in the blood, and in urine. β-hydroxybutyrate is usually not measured by the tests used to identify ketones and only acetoacetate is measured. As the acidosis improves, more β-hydroxybutyrate is oxidised to acetoacetate. Paradoxically, the measured ketones may rise after initiation of therapy though the levels of total ketones may get smaller. The total leukocyte count may also be increased to values as high as 25,000/mm^3 without any evidence of infection. Since infections are a known precipitating factor in DKA, their presence should be excluded. An important clue to the presence of an infection is a white cell count in excess of 25,000/mm^3 with a leftward shift. A persistently elevated white blood cell count after adequate therapy is also suggestive of an infection. Fever may not be present despite the presence of an infection in the acutely ill patient with DKA.

The cornerstones of therapy in DKA are fluid administration and insulin. Fluids should be administered as isotonic saline to replete extracellular volume rapidly. In an adult about 1 litre of 0.9% NaCl should be given in the first hour, with the total requirements depending on the degree of dehydration. In most patients the total fluid replacement required is about 100 ml/kg or 6–8 litres for an adult. This may be accomplished over the first 16–24 hours. Since total body potassium is depleted and insulin therapy causes intracellular flux of potassium, potassium should be added to the parenteral fluids as soon as the serum potassium is in the normal range. Serum potassium may be elevated at presentation due to the severe metabolic acidosis. The usual concentration of potassium in intravenous fluids is 20–30 mEq/L.

Insulin therapy should be initiated at the outset. Since rapid action is desired, regular insulin should be given as a continuous intravenous infusion. If this is not possible due to non-availability of equipment required to ensure accurate insulin delivery, hourly intramuscular injections of insulin can be used. There is some evidence that hourly injections of subcutaneous insulin are as effective as intramuscular insulin and are also less painful and less apt to cause tissue necrosis. It has been seen that regular insulin in a dose of 0.1 units/kg/hour allows for optimal lowering of blood sugar. This dose should be used initially. If the reduction in blood glucose is inadequate (<50–75 mg/dL/hr), the dose may be increased and patients may need upto 1 unit/kg/hr. Aggressive insulin therapy as mentioned above should be carried out until all ketones are either metabolised or excreted. Insulin administration prevents further formation of ketones. Usually the blood glucose levels are controlled before the ketones, and hence it becomes necessary to switch from normal saline to 5 per cent dextrose infusion when the blood glucose values approach 200 mg/dL. This switch serves to avoid hypoglycemia and allows for continued insulin therapy.

Despite the presence of severe acidosis, there is no indication for the use of bicarbonate in patients with DKA and there is data from clinical studies that it does not improve outcome.

Phosphate levels are also low in patients with DKA but there is no clinical evidence that replacement of phosphate improves prognosis in any way.

One of the important and potentially fatal complications of DKA particularly in the pediatric patient, is cerebral edema. This is thought to be a result of therapy, as treatment causes rapid reduction in extracellular osmolality to normal levels, while intracellular osmolality within the cerebral neurons may still be high. This leads to rapid osmotic shift of water intracellularly leading to cerebral edema. The development of this complication is one of the reasons for advocating gradual fluid replacement in children. Other complications such as hypokalemia and hypoglycemia can be avoided by frequent laboratory monitoring of serum chemistry in patients undergoing treatment.

Hyperosmolar hyperglycemic non-ketotic coma

This disorder occurs more commonly in the middle-aged or elderly person with NIDDM and uncontrolled hyperglycemia. The hyperglycemia causes an osmotic diuresis, and if the patient fails to keep his water intake adequate, severe dehydration associated with confusion and coma may occur. Since ketoacidosis with its associated symptoms of nausea, vomiting and air hunger do not occur in this condition, the patient presents late with severe hyperglycemia [often in the range 55 mmol/L (1000 mg/dL)], and extreme dehydration. The serum osmolality is very high. The serum osmolality can be estimated from the formula:

$2 \times ([Na^+]+[K^+])$ mmol/L + glucose (mmol/L) + BUN (mmol/L)

(Note : This is an approximation. The sum of sodium and potassium is doubled since it is assumed that the osmolality of anions and cations in the serum is equal. The conversion of glucose from mg/dL to mmol/L is obtained by dividing the former by 18, as 180 is the molecular weight of glucose. The BUN in mg/dL is divided by 57 to get the mmol/L amount – this generally contributes a small amount to the total osmolality).

The typical laboratory findings, besides hyperglycemia and hyperosmolality, include prerenal azotemia, and mild metabolic acidosis secondary to the prerenal failure and starvation ketosis in the comatose patient. Sometimes lactic acidosis is present concomitantly, and in this situation the metabolic acidosis is more severe.

The precipitating factors for this condition include an acute illness in the diabetic which worsens hyperglycemia and worsens water intake, such as a stroke or an infection. Once the disorder has set in the mortality is high, often above fifty per cent.

Treatment should be initiated promptly and includes the administration of fluids and insulin along with additional supportive measures. Fluids should be given as normal saline, and 2–3 litres may be given over the first 1–2 hours. The total fluid deficit to be corrected may be over 10 litres. As the plasma glucose approaches normal levels, 5 per cent dextrose should be given as a vehicle for free water administration.

With the administration of fluids alone there is considerable improvement in blood glucose levels, but insulin therapy is generally added to control the hyperglycemia more rapidly. Potassium salts are added to the intravenous fluids as the serum potassium levels start to fall.

Hypoglycemic coma

Hypoglycemia is more common in diabetics than any other group and is a result of therapy. It occurs more frequently with the use of insulin, but can also occur with sulphonylureas. It is not known to occur with the biguanides.

Most episodes of hypoglycemia are mild and are treated by the patients themselves. For this reason all diabetics who are started on therapy should be familiarised with the common symptoms of hypoglycemia; these include the adrenergic symptoms of a feeling of hunger, palpitations, sweating, and tremulousness. Other symptoms which are not related to the autonomic nervous system include confusion and eventual loss of consciousness; these are called the *neuroglycopenic* symptoms. Unfortunately, some long standing diabetics with autonomic neuropathy do not have the warning signs of hypoglycemia and the first indication of this condition is an alteration of consciousness. It has also been shown that those who have frequent episodes of hypoglycemia lose their ability to initiate an autonomic response and hence are more prone to future episodes of hypoglycemia. Therefore, it has often been said that 'hypoglycemia begets hypoglycemia'.

In any known patient with diabetes who presents with altered sensorium, hypoglycemia must first be excluded. If there is any doubt, little harm is done by giving a small dose of intravenous glucose (50 ml of 50% dextrose) before the results of definitive laboratory tests are available. When hypoglycemic coma is the diagnosis, parenteral glucose should be given till the patient regains consciousness and starts to eat. In drug-induced hypoglycemia the hypoglycemia may be prolonged. A unique situation is seen in the diabetic who takes insulin and consumes alcohol. These persons may be more prone to hypoglycemia if they skip a meal since ethanol blocks hepatic gluconeogenesis. Other aspects of hypoglycemia are discussed in the next section.

HYPOGLYCEMIA

Hypoglycemia is a condition in which the serum glucose level is below the range which is considered normal. However, there is no single number which is considered the lower limit of normal for serum glucose under all circumstances. For example, the lower limit of normal for glucose after an overnight fast varies between 60 and 75 mg/dl (3.3–4.2 mmol/L) depending on the authority quoted. After 48 hours of fasting, the median glucose for adult women in one study was only 46 mg/dl (2.6 mmol/L). After a 75 glucose load, 10–30 per cent of normal subjects will have at least one glucose level below 50 mg/dl (2.8 mmol/L) without any symptoms of hypoglycemia. Preventing hypoglycemia is critically important for human survival because glucose is the primary energy source of the brain.

Pathophysiology Ingestion of carbohydrate and protein stimulates insulin secretion by the pancreas. The insulin stimulates lipoprotein lipase activity which contributes to fat storage in the adipose tissue. Insulin also stimulates protein and glycogen synthesis in muscles, and glycogen synthesis in the liver. Several hours after eating, insulin levels fall to basal values and the body shifts from the anabolic phase to the catabolic

phase of metabolism. Serum glucose levels are initially maintained by breakdown of glycogen in the liver. In well-fed individuals, hepatic glycogen stores can maintain serum glucose levels for 8–10 hours. After glycogen is depleted, gluconeogenesis in the liver provides the body's primary defense against hypoglycemia. Pyruvate, lactate, and amino acids released from muscle as well as glycerol derived from the breakdown of fat in adipose tissue provide the substrate for hepatic gluconeogenesis. The counterregulatory hormones glucagon, epinephrine, growth hormone, and cortisol stimulate the muscle and fat catabolism which is critical for gluconeogenesis to proceed. With prolonged fasting, the kidney also becomes an important gluconeogenic organ.

During fasting most of the tissues of the body change from glucose to free fatty acids as their primary source of energy. This helps to conserve glucose for the brain which is not able to use fatty acids as its primary energy source. However, the brain is able to use ketone bodies (acetoacetic and β-hydroxybutyric acid) as energy sources. Ketone production by the liver requires several hours. Therefore, ketosis does not provide a defense for the brain from acutely developing hypoglycemia. Individuals will develop symptoms of central nervous system dysfunction from acutely developing hypoglycemia (that is, an insulin injection) at significantly higher serum glucose levels than when hypoglycemia develops gradually (that is, during prolonged fasting).

Symptomatology Symptoms of hypoglycemia are either due to adrenergic discharge or lack of glucose delivery to the brain (neuroglycopenia). Epinephrine release generally occurs before symptoms of neuroglycopenia develop. However, individuals with longstanding diabetes mellitus may develop autonomic neuropathy and lose the warning signs of the adrenergic symptoms before neuroglycopenia develops. The major adrenergic symptoms are sweating, palpitations, shakiness, hunger, and a general sense of uneasiness. This may be confusing to the clinician, as these symptoms may also be due to anxiety, stress, or panic attacks. Neuroglycopenic signs and symptoms include dizziness, ataxia, confusion, sleepiness, decreased mental acuity, convulsions, and syncope. In individuals with cerebrovascular disease, neuroglycopenia may also present with focal neurological signs and symptoms which may mimic those of a transient ischemic attack or stroke. Symptoms of hypoglycemia generally develop if an individual's blood sugar is lowered to below 45 mg/dl (2.5 mmol/L) acutely. If hypoglycemia develops gradually, such as during a 72-hour fast, symptoms of hypoglycemia may not be seen in normal women until serum glucose is below 20 mg/dl (1.1 mmol/L).

Fasting hypoglycemia

Fasting hypoglycemia needs to be differentiated from *postprandial* or *reactive* hypoglycemia which occurs 1–5 hours after a person consumes food. In contrast to individuals with fasting hypoglycemia, individuals with postprandial hypoglycemia generally do not suffer from a serious underlying disorder and do not experience major episodes of neuroglycopenia. The most common causes of hypoglycemia are summarised below.

A. Fasting hypoglycemia
- Liver disease
- Hypothermia
- Kidney failure
- Adrenal insufficiency and hypopituitarism
- Drugs—alcohol, propranolol, pentamidine, and disopyramide
- Insulin or sulphonylurea therapy of diabetics
- Factitious use of insulin or sulphonylureas
- Insulinomas
- Immune disorders with antibodies to insulin or insulin receptors
- Non-islet cell tumours– sarcomas and adenocarcinomas of adrenal, renal, or hepatic origin
- Endotoxic shock

B. Postprandial hypoglycemia
- Alimentary
- Impaired glucose tolerance
- Functional

Fasting hypoglycemia is usually due to decreased production of glucose by the liver, overutilisation of glucose outside of the liver, or to a combination of these two processes. Primary hepatic disorders such as cirrhosis, fulminant hepatitis, massive tumour infiltration, or passive congestion of the liver due to right-sided congestive heart failure may all cause hypoglycemia. Hypothermia may also cause hypoglycemia by decreasing the kidney's contribution to gluconeogenesis as well as by decreasing the catabolism of endogenous or exogenous insulin and the delivery of gluconeogenic substrates to the liver. Primary adrenal insufficiency may cause hypoglycemia due to cortisol deficiency. Individuals with hypopituitarism will be deficient in cortisol and growth hormone, both of which are important in the body's defense against hypoglycemia. Various drugs, most prominently alcohol, may decrease hepatic gluconeogenesis. Alcohol-induced hypoglycemia occurs only after a period of restricted caloric intake long enough to deplete hepatic glycogen stores. Individuals, particularly diabetics, should be advised to eat whenever they drink alcoholic beverages. Propranolol and other non-cardioselective beta-blockers may cause hypoglycemia by blocking adrenergic-stimulated glycogenolysis. These medications are particularly dangerous in insulin treated diabetics.

Fasting hypoglycemia may also be due to overutilisation of glucose. This occurs in situations where excess insulin is present such as in insulin- or sulphonylurea-treated diabetics, individuals with insulin-secreting tumours, individuals with psychiatric disorders who surreptitiously take hypoglycemic agents, or the rare patient with an autoimmune disorder with antibodies to insulin. Individuals with antibodies which bind insulin may release insulin at inappropriate times leading to hypoglycemia. Sepsis with endotoxemia may cause hypoglycemia presumably due to excess insulin secretion stimulated by sepsis-associated cytokines. Several drugs such as the antipneumocystis agent pentamidine, or the antiarrhythmic agent disopyramide may cause hypoglycemia by stimulating insulin secretion.

Finally, there are several causes of hypoglycemia due to overutilisation of glucose which are not insulin mediated. Several non-islet cell tumours may cause hypoglycemia, most commonly by secreting peptides which have insulin-like actions. Various sarcomas and abdominal carcinomas are the most common non-islet cell tumours which cause hypoglycemia. Some individuals with autoimmune disorders have antibodies to the insulin receptor. These antibodies may cause diabetes if they block the receptor. The antibodies in other individuals will cause hypoglycemia due to activation of insulin receptors.

In order to diagnose hypoglycemia, *Whipple's triad* must be fulfilled. This includes low serum glucose in association with typical symptoms of hypoglycemia which are relieved by increasing glucose levels. The most important test to diagnose hypoglycemia is a low blood sugar value when the patient has typical symptoms. The most important procedure in the evaluation to determine the cause is a prolonged fast. In one series, 95 per cent of patients with insulinoma developed symptomatic hypoglycemia within 48 hours. If the fast is prolonged to 72 hours virtually all insulinoma patients will have symptomatic hypoglycemia. It is critical to obtain a serum insulin level and a simultaneous blood sugar during fasting when an individual develops hypoglycemic symptoms. Serum insulin levels generally reach basal levels after blood sugar drops below 83 mg/dl (4.6 mmol/L). Ratios of insulin (in μU/ml) to glucose (in mg/dl) above 0.3 are generally considered to be abnormal. Individuals with insulinomas have relatively high serum proinsulin levels. Normally, proinsulin comprises up to 20 per cent of the insulin-like immunoactivity in an individual. Other less widely used diagnostic tests for insulinoma include the C-peptide suppression test using

exogenous insulin and the tolbutamide stimulation test.

When approaching a non-diabetic patient with spontaneous hypoglycemia in the emergency room, it is important to obtain blood for C-peptide, insulin antibodies, and plasma or urine sulphonylureas levels. *Factitious hypoglycemia* due to surreptitious use of insulin or sulphonylureas must be suspected in medical personnel or in families of diabetic individuals. These individuals will have suppressed C-peptide levels in association with elevated insulin levels if they have been taking exogenous insulin. C-peptide is normally produced during insulin biosynthesis when it is excised from proinsulin. Individuals with insulinomas and factitious self-injection of insulin will both have high serum insulin levels. However, C-peptide levels will be high in individuals with insulinomas but low in individuals who have taken insulin. Individuals, who have factitious hypoglycemia due to intake of hypoglycemic drugs will have high C-peptide levels also. They can be accurately diagnosed by their high serum or urine sulphonylurea levels. The presence of insulin antibodies in a non-diabetic individual suggests factitious injection of insulin or an autoimmune disorder with insulin antibodies.

Once an insulinoma has been diagnosed biochemically, an anatomical search for the tumour must be launched. These tumours are frequently benign and small (<2 cm). Only 10 per cent are malignant. Selective angiography will localise the tumour in 80 per cent of cases. Localisation may also be accomplished by percutaneous transhepatic venous sampling for insulin levels or by intraoperative ultrasound. If surgical therapy of an insulinoma is unsuccessful, medical therapy with diazoxide, which blocks insulin release, may be attempted. In the occasional patient with a malignant insulinoma chemotherapy with adriamycin and streptozocin may be utilised.

Postprandial hypoglycemia

Postprandial hypoglycemia refers to hypoglycemia occurring in a predictable pattern with respect to meals in any one individual. Whipple's triad must be fulfilled in order to make a definite diagnosis of postprandial hypoglycemia. Patients who have had gastric surgery (most commonly a subtotal gastrectomy) for peptic ulcer disease have an increased rate of transit of gastric contents from the stomach into the small intestine. This may result in a rapid increase of plasma glucose which elicits insulin hypersecretion. Glucose concentrations may fall more rapidly than insulin under these circumstances leading to hypoglycemia, occurring most commonly 2 hours after eating. Occasional individuals with glucose intolerance without overt diabetes may manifest true reactive hypoglycemia. This entity typically occurs 4–6 hours after eating and is related to an exaggerated second phase insulin secretion. Finally, occasional subjects will have true reactive hypoglycemia despite no apparent underlying disorder. However, the vast majority of individuals who think they have reactive hypoglycemia have what has been called pseudohypoglycemia. This refers to a group of subjects who develop adrenergic symoptoms several hours after eating, but do not fulfill Whipple's triad for true hypoglycemia. These subjects may have had *five-hour oral glucose tolerance tests* (OGTT) which label them as being hypoglycemic. However, as mentioned above upto 30 per cent of normal individuals may have a plasma glucose level < 50 mg/dl (2.8 mmol/L) during a 5-hour OGTT. For this reason the OGTT should be abandoned as a diagnostic test for postprandial hypoglycemia. Measuring serum glucose levels after ingestion of a normal mixed meal is a more rational approach to establishing the diagnosis of postprandial hypoglycemia. If the diagnosis is established, the patient should be advised to eat small, frequent meals, and to restrict the intake of simple carbohydrates.

16.9 Disorders of sexual differentiation

Almost all individuals are perceived as being either male or female. The differentiation into the two distinct sexes involves three components —the *chromosomal* sex, the *gonadal* sex, and the *phenotypic* sex. The chromosomal make-up of an individual determines the gonadal sex, which in turn determines the phenotypic development of the male or female urogenital tract and the external genitalia. However, sometimes abnormalities in this normal development occur due to chromosomal abnormalities, hormonal aberrations and environmental insults. This results in conditions where the gonads may be abnormal, or there are phenotypic abnormalities in sexual differentiation despite the presence of normal gonads.

Classification of disorders of sexual development

A. **Disorders affecting gonads**
   - True hermaphroditism
   - Gonadal dysgenesis
   - Turner syndrome
   - Klinefelter syndrome

B. **Disorders affecting ductal systems**

C. **Disorders affecting the external genitalia (normal gonads)**
   - Female pseudohermaphroditism
   - Male pseudohermaphroditism

Normal sexual differentiation

Early in embryogenesis the gonads of both sexes are indifferent and *bipotential*. This means they can develop into ovaries or testis depending on the stimulus they receive. During the fifth week of development the *primordial* (primitive, undifferentiated) *germ cells* migrate to the *gonadal ridges*. By about seven weeks of gestation, the gonads differentiate towards testicular or ovarian development, depending on the genetic factors mentioned below.

Genes on the X and Y chromosomes and the autosomes[1] are important for sexual differentiation. The study of individuals with disorders of sexual differentiation has given us clues that the Y chromosome is important for testes formation. The gene on the Y chromosome which is important for the development of the testes has been identified and named the *sex determining region Y* or the SRY. The presence of the SRY gene appears to be important in the formation of the testes from the bipotential genetic ridge in the embryo. This gene has been cloned and the protein made by it has been characterised. This protein is similar to a group of proteins which control the transcription of DNA and hence regulate gene expression. The protein product of the SRY gene has been shown to downregulate expression of the *p450 aromatase gene* which converts testosterone to estrogen, and also interacts with the *antimullerian hormone gene* which is responsible for the regression of the mullerian ducts. There are other gene(s) on the chromosome and autosomes, which are responsible for normal testicular development.

[1] Autosomes are the other 22 pairs of chromosomes.

In the absence of the Y chromosome the onadal ridge develops into an ovary. Because he absence of the Y chromosome is all it takes or the gonads to develop into an ovary, even a ingle X chromosome [i.e., monosomy X [45,X)] s sufficient for ovarian development. The bsence of the second X chromosome, however, auses the ovarian follicles in 45,X persons to ecome atretic at an accelerated rate. Thus, the econd X chromosome seems to be important or ovarian maintenance rather than ovarian ifferentiation.

The subsequent differentiation of the ductal ystems unique to the sexes depends on the ynthesis of hormonal factors secreted by the estes. They are testosterone and the *ntimullerian hormone* (AMH). Testosterone is roduced by the *Leydig cells* in the testes, and timulates the development of the *Wolffian duct* ystem to form the epididymis, the vasa deferentia and the seminal vesicles. It also acts ocally to stimulate the differentiation of the glans penis and the corpora cavernosa from the *genital tubercle,* and the formation of the corpora spongiosa and the scrotum. Testosterone also stimulates the formation of the prostate and *Cowper glands.* The *antimullerian hormone* is synthesised by the *Sertoli cells* in the testes and acts to cause regression of the *mullerian ducts.* It may also have a role in testicular descent. In the absence of testicular formation and the production of testosterone and antimullerian hormone, the Wolffian ducts regress and the mullerian ducts develop into the uterus, fallopian tubes and upper vagina. Absence of testosterone also leads to the development of the female external genitalia. The *genital tubercle* gives rise to the clitoris, the *urethral folds* to the labia minora, the labioscrotal swellings to the labia majora, and the *urogenital sinus* to the lower two-thirds of the vagina. The gonaductal and genital differentiation in females does not require any factors secreted by the ovary, as castrated 46, XY embryos also develop into females.

Disorders of Sexual Differentiation

Whenever a patient with abnormal sexual differentiation presents, it is important to carry out a detailed physical examination including assessment of the external genitalia and secondary sex characteristics to determine the phenotypic sex. It is also usually necessary to obtain a karyotype analysis which gives information about the chromosomal make-up. Rarely, genetic studies may be indicated to study mutations or deletions of genes important in sexual differentiation. On the basis of the above information it is usually possible to assign the person to a previously-defined category. In patients seen at an older age, the *gender of rearing* till the time of seeking medical advice is important since treatment must be geared towards preserving this *gender identity.* It is easiest to consider such disorders on the basis of whether they involve primarily the gonads, the ductal structures involving the gonads, or the external genitalia.

Errors in Gonadal Development

True hermaphroditism

True hermaphrodites are rare. By definition, they possess both testicular and ovarian tissue or a common *ovotestes.* Most true hermaphrodites are genetically 46,XY but they can be 46,XY or mosaics such as 46,XX/46,XY or 46,XX/47,XXY. It is uncertain as to why a 46,XX karyotype should be associated with development of testicular tissue as the SRY gene occurs on the Y chromosome (see above). An explanation for this is undetected *chimerism,* that is, the presence of two or more cell lines with different karyotype in the same individual. Therefore, a true hermaphrodite with 46,XX karyotype may have cells of the 46,XY karyotype in some parts of their body. Other explanations include translocation of the SRY gene to an autosome or X chromosome, or activation of other sex reversal genes.

The external genitalia can be male, female, or ambiguous, that is, female with some male

features. Breast development may occur at puberty despite the presence of male external genitalia. The gonads may be located in the testicular position, and have varying amounts of testicular and ovarian tissue (ovotestes). Uterine horns may develop on the side where ovarian tissue is present, leading the person to menstruate. The patient may be reared either as a male or female, and appropriate reconstructive surgery may be undertaken. All gonadal tissue should be biopsied and tissue not compatible with the gender assignment should be removed.

Gonadal dysgenesis

Dysgenesis implies the absence of germ cells in the gonads. When the germ cells are absent in the ovary, they appear as small *fibrous streaks* in the position normally occupied by the ovary. In the testes, gonadal dysgenesis is associated with a smaller size of the testes and with abnormal seminiferous tubules.

Ovarian dysgenesis

The common phenotype described in patients of ovarian dysgenesis is the Turner syndrome.

Some individuals with streak gonads do not have the other somatic anomalies described in Turner syndrome. Individuals with ovarian dysgenesis most commonly have the 45,X karyotype, that is, the second sex chromosome is missing.

Most fetuses with this chromosomal abnormality are spontaneously aborted in the first trimester of pregnancy; about 20 per cent of chromosomally abnormal abortuses have monosomy X. Individuals born with monosomy X have a female phenotype as is expected in the absence of a Y chromosome. It has been seen that these people have normal germ cell formation and oocytes can be seen in their ovaries at birth. However, there is increased oocyte atresia in the absence of a second X chromosome. According to the *Lyon hypothesis*, all X chromosomes in excess of one are inactivated. Hence, it is unclear why 45,X individuals should have atresia of oocytes and abnormal development. It is likely tha inactivation of the second X does not occur i human oocytes, and that even at other site certain loci of the second X chromosome remai active.

In 45,X individuals the lost second se chromosome is due to the non-contribution o this chromosome by the father. For this reason maternal age is not increased in 45, X fetuses.

Individuals with ovarian dysgenesis do no exhibit secondary sexual characteristics. Pubi and axillary hair are scanty. Breast developmen is poor and the uterus and vagina remain smal Streak ovaries lead to reduced estrogen an androgen levels and there is an associate increase in follicle stimulating hormone (FSH and luteinising hormone (LH) levels. Thi picture in association with certain other somati abnormalities has been described as the Turne syndrome.

Features of Turner syndrome are

- Short stature, short webbed neck
- Low nuchal (over the neck) hairline
- Mild mental subnormality
- Widely spaced nipples, rectangular contour o chest (shield chest)
- Skeletal abnormalities
- Cubitus valgus—wide carrying angle
- Short fourth metacarpal
- Kyphoscoliosis
- High arched palate
- Cardiac anomalies—coarctation of aorta
- Renal anomalies—horseshoe kidneys
- Pigmented nevi, lymphedema

Deletion of the long or short arms of chromo some X may also cause gonadal dysgenesis i association with the other features of Turne syndrome. Individuals with mosaicism involvin X chromosomes may have the karyotyp 45,X/46,XX.

These individuals have some anomalie characteristic of Turner syndrome, but they ma be less severely affected than the classical Turne patient. Gonadal dysgenesis sometimes occurs i

individuals with the 46,XX karyotype. These individuals are phenotypic females with normal stature but may have other Turner characteristics. The pathogenetic mechanism for this disorder is not known, and there seems to be an autosomal recessive pattern of inheritance.

Mixed gonadal dysgenesis is the term applied to a condition when an individual shows one streak gonad (dysgenetic ovary) and one dysgenetic testis. The testis may be in the normal position, but is frequently intraabdominal and the person is reared as a female. Most individuals have ambiguous external genitalia and usually have a uterus. This phenotype is usually associated with 45,X/46,XY mosaicism. The presence of a uterine rudiment in such individuals is of diagnostic importance to help distinguish them from *male pseudohermaphroditism* (see later), a condition in which a uterus is absent.

When Turner stigmata are present, the diagnosis of gonadal dysgenesis is made in early childhood. In neonates, suspicion should be high if lymphedema of the hands and feet is present. Other patients with the disorder are diagnosed when evaluation for short stature is sought. The diagnosis of the 45X karyotype is suspected when there is absence of the *Barr body*, which is the inactive X chromatin in females with 46,XX. Men, and women with 45,X do not have the Barr body. However, complete analysis of chromosomal karyotype is necessary to avoid missing patients with mosaicism, or deletions of the X chromosome and gonadal dysgenesis. The levels of estrogen are low and circulating gonadotrophins are elevated.

Treatment of such individuals is aimed at increasing height, and achieving sexual maturation. Growth hormone therapy has been utilised to increase final height and appears to have moderate efficacy; increases in final height of upto 6–8 cm can be achieved. However, growth hormone therapy is expensive and there is evidence that low doses of estrogens can also increase height, perhaps by increasing endogenous growth hormone levels. Combinations of growth hormone or estrogen and anabolic steroids have been used to increase height, but the mechanism by which the anabolic steroids increase height is unclear. Sexual maturation can be achieved by administering gradually increasing doses of estrogens starting at the age of 12 or 13 years. Progestins are added for the last 14 days in the month to prevent unopposed estrogen action and endometrial hyperplasia. This also leads to regular menstrual cycles. Breast tenderness is a sign of excessive estrogen. Estrogen therapy should be initiated only by experts.

Klinefelter syndrome—Seminiferous tubule dysgenesis Males with this condition have two or more X chromosomes and one Y chromosome. Most commonly patients are 47,XXY but the phenotype can be associated with 48,XXYY or 49,XXXXY and 46,XY/47XXY mosaics. The most characteristic abnormalities are seminiferous tubule dysgenesis leading to azoospermia, infertility and androgen deficiency. The testis are small, always less than 3.5 cm in length. Androgen deficiency may be associated with poor facial hair growth and eunuchoid body habitus. This body habitus is characterised by a tall stature and increase in the proportion of the *lower segment* of the body as compared to the *upper segment*. Gynecomastia may be present; it is related to a reversal of the ratio of circulating testosterone to estrogens. Other clinical features include the presence of mild mental deficiency, abnormalities of thyroid function, diabetes mellitus, obesity, and pulmonary disease.

These patients also have a higher risk of breast cancer as compared to normal men. Sometimes patients with Klinefelter syndrome present with infertility as their only complaint, and the diagnosis may not be evident till the karyotype is obtained. A clue to the diagnosis is a high LH and FSH level in the patient (suggestive of primary hypogonadism). Treatment is aimed at providing androgens (in the form of intramuscular injections of

testosterone) in order to reduce gynecomastia and to prevent the osteoporosis associated with prolonged testosterone deficiency.

Ullrich-Noonan syndrome This is also called the *pseudo-Turner* syndrome. Women with this condition have a 46,XX karyotype, but exhibit the somatic features of Turner syndrome. These include the short stature, webbed neck, lymphedema and cardiac abnormalities. However, these females have normal ovaries and are fertile. A karyotype helps in the diagnosis, and avoids the patient being labelled as Turner syndrome. Men with normal 46,XY chromosomal component may show Turner stigmata and have the male form of the Ullrich-Noonan syndrome. In contrast to the girls with the same syndrome (who have normal sexual development), boys may have undescended or hypoplastic testes and require testosterone replacement at puberty.

Errors in Ductal Development

Anomalies in the female ductal system

Abnormalities may occur at any level in the mullerian ductal system and may or may not affect fertility depending on the severity of the malformation. Abnormalities of the vagina include an *imperforate hymen*, presence of vaginal *septae* and vaginal *atresia*. All these can be treated surgically. Aplasia of the mullerian ducts leads to absence of the uterus, cervix and the upper portion of the vagina. The lower portion of the vagina develops from invagination of the urogenital sinus and ends blindly. Despite the presence of primary amenorrhea, the secondary sexual characteristics are normal. The normal development of secondary sexual characteristics helps to distinguish this condition from *testicular feminisation syndrome*, which is a condition occurring due to complete insensitivity to androgens in a genetic male (46,XY). Individuals with testicular feminisation have little or no pubic hair and have incomplete breast development. Vertebral anomalies and renal anomalies such as pelvic kidney or renal aplasia may be associated with mullerian agenesis. The normal fusion of the paired mullerian ducts leads to the formation of the uterus and the upper part of the vagina. When there is normal development of only one mullerian duct, a *unicornuate* (single horn) uterus is formed. Some of these individuals may have a non-communicating rudimentary uterine horn on the other side. Women with unicornuate uterus have a high incidence of first trimester abortions. Incomplete fusion of the mullerian ducts leads to a *bicornuate uterus* if the fusion is normal at the lower end. Complete non-fusion of the mullerian ducts leads to *uterus didelphys* (Fig 16.30).

Anomalies in the male ductal system

The absence of Wolffian derivatives may be associated with absence of the upper urinary tract, or just an isolated lack of the epididymis, ductus deferens and seminal vesicle. The gonads are usually normal. Another abnormality is a failure of fusion of the *rete cords* in the testes to

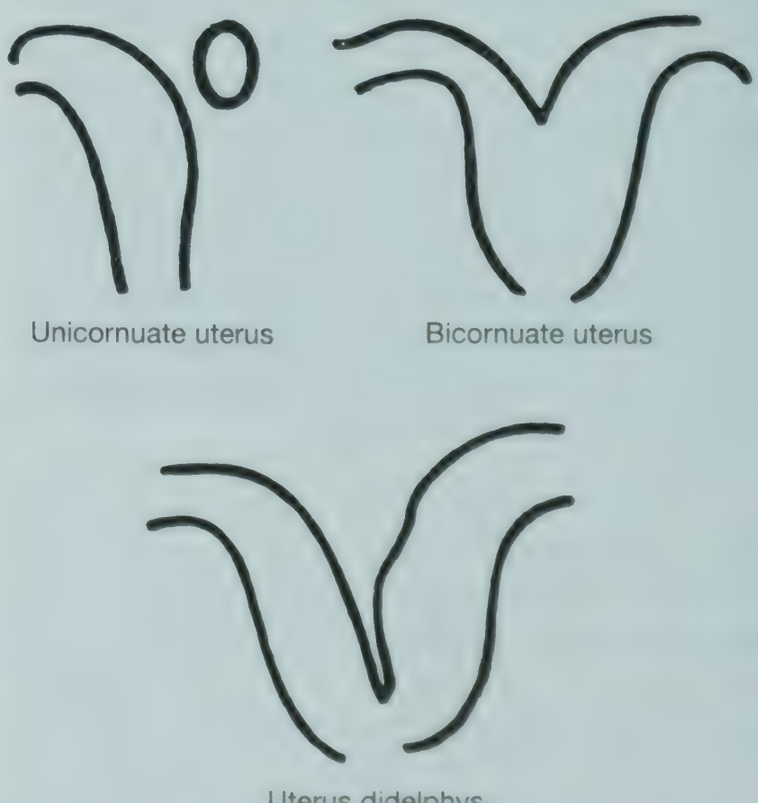


Fig 16.30

ne *ductuli efferentia* (which develop from the Wolffian system). In both the above situations if ne defect is bilateral the patient is infertile. Unilateral defects are asymptomatic. Sometimes ne testes fail to descend in individuals with nese defects. In some apparently normal men, ne uterus and fallopian tubes may persist ndetected (persistent mullerian duct syndrome: escribed later). This may be due to an nsensitivity of the mullerian structures to AMH. This condition is sometimes detected because ne uterus and fallopian tubes are sometimes etected in an inguinal hernia (uteri inguinale).

Errors in Genital Differentiation

n *pseudohermaphroditism* the individual's sex hromosomes and gonads are characteristic of ne sex, but also have some characteristic henotypic features of the opposite sex. Since ifferentiation of external genitalia occurs etween approximately 7 and 16 weeks of regnancy, the fetus is most vulnerable during his period due to certain factors which nay affect genital development. The only bnormalities which can occur, if development f the genitalia occur normally during this eriod, is clitoromegaly in women and ndescended testes in men.

emale pseudohermaphroditism

The most common cause of female seudohermaphroditism is congenital adrenal yperplasia. The basic abnormality in this ondition is the presence of a defect in the ynthesis of cortisol. This leads to hypersecretion f ACTH by the pituitary, causing hyperplasia of he adrenals. If the enzymes required to enerate adrenal androgens are intact, as they sually are, the steroid precursors for cortisol re directed towards adrenal androgen synthesis. The excess adrenal androgens cause virilisation f the female fetus in utero. It is treated by iving the patient glucocorticoids to correct the eficiency and to suppress ACTH hyper-ecretion, thereby ameliorating the hyperandro-genism. Treatment is most effective if given at 8–16 weeks, and a fetus can be screened by amniocentesis or chorionic villus sampling if there is a family history of the disorder. The three adrenal enzyme defects which cause this syndrome are 21-hydroxylase deficiency, 11-hydroxylase deficiency, and 3-hydroxy-steroid dehydrogenase deficiency. The pathways for adrenal steroidogenesis are depicted in Fig 16.19. Another cause of female pseudo-hermaphroditism is the ingestion of large doses of androgenic compounds by the mother during pregnancy.

Male pseudohermaphroditism

Defective virilisation of a male embryo can be due to androgen insensitivity, defects in androgen synthesis, or other uncertain causes.

Androgen action may be defective either due to *5α-reductase deficiency* or due to *defective androgen receptors*. 5α-reductase is an enzyme that helps in conversion of testosterone to dihydrotestosterone.

Dihydrotestosterone is important for the virilisation of the urogenital sinus and for the development of normal male external genitalia. In patients with 5α-reductase deficiency, the testes and Wolffian structures are normal, but there is severe perineoscrotal hypospadias and the urogenital sinus forms a blind-ending vagina. The patient appears to be a phenotypic female. Typically, the patient has a female habitus with absence of breast development but with normal axillary and pubic hair. This disorder is inherited with an autosomal recessive pattern.

Defect in the androgen receptor results in a phenotypic female appearance with normal breast tissue, and normal-appearing female external genitalia. The vagina is short and ends blindly, and the patient has undescended testis. Because of the complete absence of androgen action, these patients have absent axillary and pubic hair, which is an important clue to the diagnosis. Most patients present with the complaint of primary amenorrhea. This disorder is known as *testicular feminisation syndrome.*

Other disorders of the androgen receptor may cause lesser degrees of incomplete virilisation and the male phenotype may be more evident. That *Reifenstein syndrome* is one such form, where phenotypic males have perineoscrotal hypospadias and gynecomastia. Another condition known as the *infertile male syndrome*, may manifest as azoospermia in an otherwise normal-appearing male. It is estimated that a defect of the androgen receptor may be present in a fifth of men with idiopathic azoospermia. The androgen receptor gene is present on the X chromosome. Patients with feminisation due to defects in the androgen receptor gene usually have higher than normal levels of androgen.

Persistent mullerian duct syndrome is seen in phenotypically normal men who also have bilateral fallopian tubes, a uterus, and an upper vagina. These subjects may present with inguinal hernias which contain the uterus, and cryptorchidism is common. It is assumed that individuals with this abnormality either fail to produce normal amounts of mullerian inhibiting substance or do not respond to it.

CLINICAL APPROACH TO A PATIENT WITH GENITAL AMBIGUITY

The phenotypic sex should be assessed if possible and this is often a difficult task. The genetic sex should be determined at the earliest, by analysis of the lymphocytes. The analysis of buccal cells for the presence of X chromosome may be fallacious as this does not give information about the total number of X and Y chromosomes (often there are multiple copies of each), and also of specific deletions of parts of these chromosomes. A complete karyotype of chromosomes can be obtained from peripheral lymphocytes arrested in metaphase. The X and Y chromosome can be studied by *high resolution banding* to identify deletions, rearrangements, non-dysjunction and other defects. Specific regions on these chromosomes can also be characterised by using specific probes for in situ hybridisation. Many of the genes responsible fo sexual differentiation have been identified an cloned and are available as probes; these includ SRY and genes for the androgen receptor 5α-reductase, 21-hydroxylase, and antimulleria hormone. Various genetic techniques can b used to identify these genetic abnormalities.

Biochemical tests such as serum sodium an potassium and serum 17-hydroxyprogesteron are helpful in determining the presence o congenital adrenal hyperplasia. It is als recommended that AMH be measured as it is sensitive indicator of testicular tissue.

There may be certain clues on physica examination which help in the diagnosis. Th location of the urethral opening in men is at th tip of the glans penis whereas in women wit clitoral hypertrophy it remains at the base of th clitoris. In incomplete virilisation in the male, a also in androgen insensitivity, the urethra opening is located on the proximal glans peni the shaft of the penis or the perineum dependin on the severity of the disorder. In a patient wit ambiguous genitalia the presence of a uteru narrows down the list of diagnostic possibilitie to female pseudohermaphroditism, true herma phroditism or persistent mullerian duc syndrome. Frequently, the uterus can be pa pated by rectal examination, although a pelv ultrasound examination and other radiolog studies may be necessary. The finding of a gona in the labial or inguinal regions invariab indicates the presence of testicular tissue. Th finding of stigmata suggestive of Turne syndrome in a person with ambiguous genital raises the possibility of 45,X/46,XY mosaicism.

Usually, ambiguous genitalia are recognise at birth, but occasionally the condition may b recognised only in infancy or childhood. Th issue of changing the sex of rearing may the arise – this is usually not a problem if don before 2 years of age, but a change in sex beyon this age may lead to psychological problem Surgical procedures are available to make th external genitalia compatible with th appropriate sex chosen for the child.

KEY CONCEPTS

Turner syndrome

- ➢ In Turner syndrome, a 45XO karyotype results in gonadal dysgenesis.
- ➢ Phenotypic features include a short webbed neck, shield-like chest and sexual infantilism.
- ➢ Treatment includes estrogen-progesterone therapy.

Klinefelter syndrome

- ➢ Klinefelter syndrome is a disorder associated with a 47, XYY karyotype and primary testicular failure.
- ➢ Phenotypically, the affected males have small testes, infertility, gynecomastia and a variable reduction in libido and potency.
- ➢ Diagnosis requires chromosomal analysis, increased LH/FSH levels, low testosterone, and azoospermia (>90%).
- ➢ Treatment consists of androgen replacement.

16.10 Disorders of metabolism

Disorders of Acid-Base Balance

The normal pH of the extracellular fluid ranges from 7.35 to 7.45 in health. The pH is maintained in this narrow range by matching the input of acid or base into the body with the output of acid or base. The endogenous acids consist of *volatile* and *non-volatile* acids. The volatile acids are produced at a daily rate of 22,000 mEq of hydrogen ion, principally from combustion of glucose and fatty acids (yielding carbon dioxide and water). The non-volatile acids are principally derived from the metabolism of sulphur-containing amino acids and the daily production rate is about 1 mEq/kg body weight. This daily acid load is buffered by the body's buffering mechanisms; the *bicarbonate buffer* system is one of the principal buffer systems in the body. The bicarbonate found in plasma and in erythrocytes accounts for more than 50 per cent of the buffering capacity of blood. The *non-bicarbonate buffers* in blood include the hemoglobin system and plasma proteins. *Tissue buffers* include the bicarbonate within muscle cells and in the bones; these tissue buffers neutralise about five times as much acid as the blood buffers. The bicarbonate buffer system neutralises only the non-volatile acids. The hemoglobin system neutralises most of the volatile acids.

The bicarbonate buffer system in the extracellular fluid is regulated by the kidneys in several ways. The kidneys reabsorb filtered bicarbonate at the proximal convoluted tubules. Bicarbonate reabsorption is increased by potassium depletion, chloride depletion or by an increase in P_aCo_2.

Determination of acid-base disorder type

Clinical disturbances of acid-base metabolism are defined in terms of the bicarbonate buffer system. Metabolic acidosis and alkalosis are discussed below.

Acid-base disorders cannot be diagnosed accurately from their clinical picture alone. Arterial blood gases[1] are, therefore, essential and central to the diagnosis of acid-base disorders. Determination of pH, P_aCO_2 and HCO_3 are required for ascertaining the type of disorder (Table 16.20). Fig 16.31 shows a simplified approach to a patient with suspected acidosis or alkalosis. Additionally estimation of serum sodium and chloride levels help characterise the etiology of metabolic acidosis.

Although an arterial sample is the most appropriate specimen to assess blood gases, it should be pointed out that, unless there is an emergent situation such as cardiac arrest, a venous sample can also provide important clues when combined with arterial oxygen saturation values obtained from a *pulse oximeter*. Venous blood pH is usually only 0.03–0.04 units lower than that of arterial blood, and venous blood PCO_2 is only 7–8 mmHg higher. Calculated bicarbonate concentration in venous blood is at most 2 mEq/L higher than that of arterial blood.

[1] Obtained by arterial puncture with a syringe coated with 1 ml of heparin and followed by immediately capping the needle with a rubber cap. Note that excess heparin can falsely lower the pCO_2 and HCO_3

Table 16.20 Classification of acid-base disorders based on arterial blood gas analysis

pH	*pCO_2* Low (<35 mmHg)	Normal (40±5 mmHg)	High (>45 mmHg)
Low (<7.35)	primary metabolic acidosis + either incomplete respiratory compensation OR coexistent respiratory alkalosis	primary metabolic acidosis	primary respiratory acidosis + either incomplete metabolic compensation OR coexistent metabolic alkalosis
Normal (7.40±0.05)	primary respiratory alkalosis + compensatory metabolic acidosis	normal	Respiratory acidosis + compensatory metabolic alkalosis
High (>7.45)	primary respiratory alkalosis (with or without coexisting metabolic alkalosis)	primary metabolic alkalosis	Primary metabolic alkalosis + Coexisting respiratory acidosis

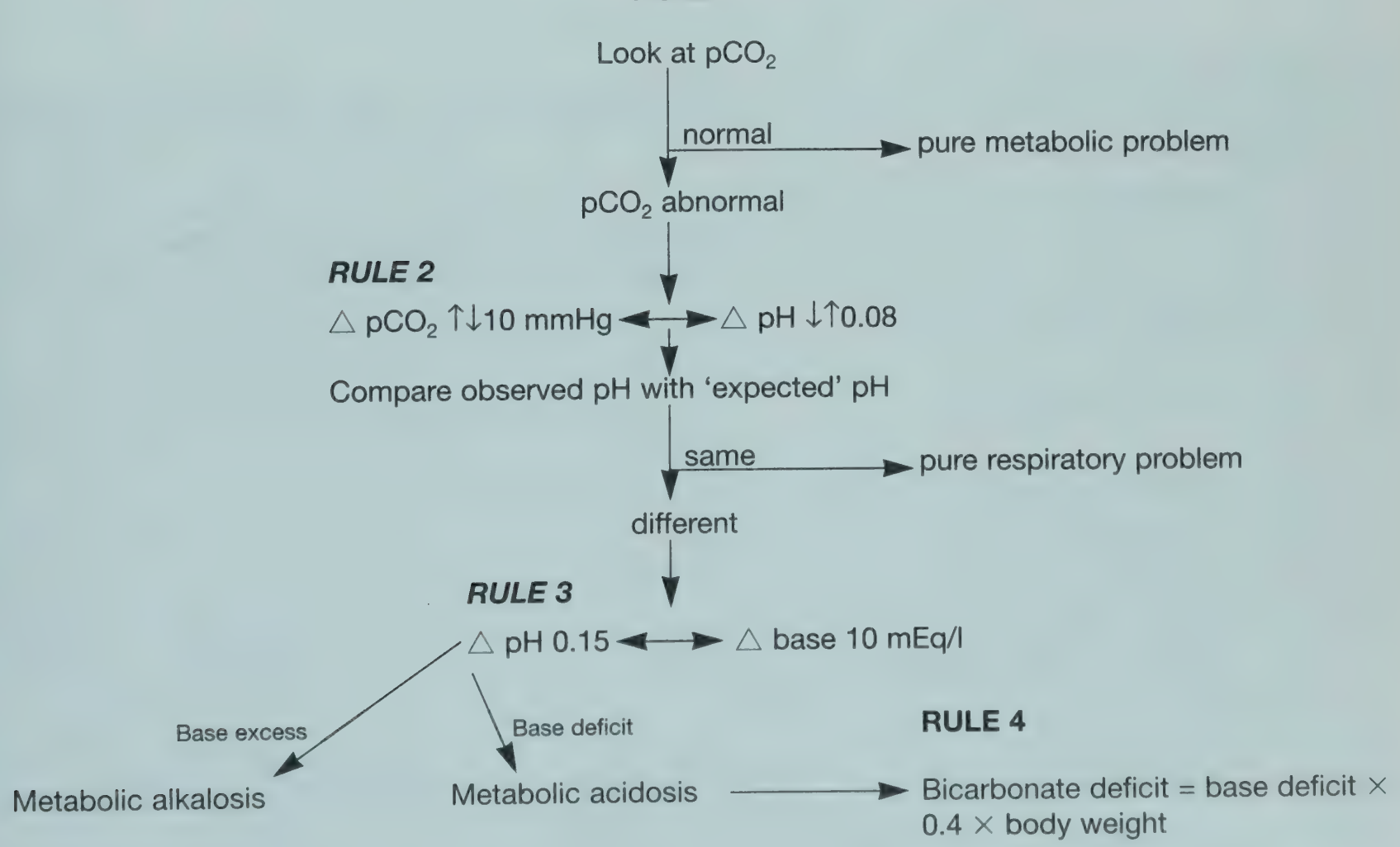


Fig 16.31 Diagnosis of acid-base disorders

Metabolic Acidosis

Metabolic acidosis is defined as a physiologic state characterised by excess of acid in the body relative to bases resulting in a pH <7.35 along with a normal or low PCO_2 (<40 mmHg in the absence of lung disease). The causes of metabolic acidosis and the treatment are summarised in Table 16.21. Briefly, they include conditions resulting in increased production of acids, a decreased excretion of acids or an increased loss of bases from the body. The concept of *anion gap* was introduced in the management of diabetic ketoacidosis. The presence of an *increased anion gap* suggests accumulation of unmeasured anions (such as ketoacids in diabetic ketoacidosis, sulphate in renal failure, lactate in lactic acidosis). The presence of a *normal anion gap* usually indicates bicarbonate loss, either through gastrointestinal tract or in urine.

The initial clinical symptoms of metabolic acidosis include headache, lethargy, lassitude and nausea. As the pH drops further, there is drowsiness, vomiting, and an increse in the depth of respiration. Later as the lungs try to compensate by 'blowing off' CO_2, the frequency of respiration also increases (classical *Kussmaul's breathing*). The sensorium deteriorates and the patient becomes stuporose. With severe acidosis, a state of circulatory shock supervenes, due to impaired myocardial contractility and the patient becomes comatose.

The treatment of acidosis depends on its severity and its etiology. The treatment of various conditions causing acidosis is also summarised in Table 16.21. The hydration status, serum levels of other electrolytes (notably potassium) must be evaluated and corrected along with correction of acidosis. This is important as correction of acidosis leads to shift of potassium into the cells with consequent hypokalemia, which may be life-threatening.

Table 16.21 Causes of metabolic acidosis (with treatment)

Etiology	*Treatment*
A. With increased anion gap	
1. Renal failure	Chronic renal failure: usually mild, no treatment; if HCO_3^- <15 mmol/L, oral alkali Acute renal failure: no specific therapy, resolves with dialysis
2. Diabetic ketoacidosis (DKA)	Insulin for DKA; no specific treatment for acidosis; if HCO_3^- <8 mmol/L or pH<7.1, i.v. bicarbonate
3. Alcoholic ketoacidosis	Glucose and saline for ketoacidosis; no specific treatment for acidosis
4. Starvation ketoacidosis	Mild acidosis, requires no treatment
5. Lactic acidosis	Treat underlying cause; if HCO_3^- <8 mmol/L or pH <7.1, i.v. bicarbonate
6. Exogenous agents (methanol, paraldehyde, salicylates)	Stop agent; specific treatment for agent; if HCO_3^- <8 mmol/L or pH <7.1, i.v. bicarbonate
B. With normal anion gap	
1. Renal tubular acidosis	Proximal RTA: usually no treatment for acidosis required Distal RTA: oral alkali required
2. Gastrointestinal loss of alkali (diarrhea)	Treat losses with oral/intravenous fluids
3. Drugs (acetazolamide, ammonium chloride)	Stop offending drug

If acidosis is acute and severe (pH <7.10), arenteral therapy with sodium bicarbonate is ndicated. The amount of bicarbonate deficit is alculated as the base deficit multiplied by 0 per cent of the body weight. About half the eficit can be replaced over 3–4 hours unless eart failure is present. Once the pH reaches .20, no further bicarbonate should be given. Bicarbonate is usually replaced by adding –3 ampoules of 7.5% solution (44.6 mEq/ mpoule) to a litre of 5% dextrose.

Metabolic Alkalosis

Metabolic alkalosis is defined as a physiologic tate characterised by excess of base in the body elative to acids resulting in a pH >7.45 along vith a normal or high PCO_2 (>45 mmHg). The auses of metabolic alkalosis are sum-marised elow. Briefly, they include conditions with xcess loss of acids or with excess retention of ases. The excess loss of acids may be from the gastrointestinal tract (vomiting, fistulae) or the idneys (mineralocorticoid excess). Excess etention of bicarbonates may arise from an xcess oral intake (antacids, absorbable alkali) r intravenous overenthusiastic repletion.

Causes of metabolic alkalosis

A. Saline-responsive alkalosis (U_{Cl^-}<10 mEq/day)
  1. Gastrointestinal loss
     vomiting
     nasogastric suction
  2. Diuretic therapy (thiazides and loop diuretics)
  3. Exogenous alkali (transfusions, milk-alkali syndrome)
  4. Posthypercapneic

B. Saline-unresponsive alkalosis (U_{Cl^-} >10 mEq/day)
  1. Mineralocorticoid excess states
     Conn syndrome
     Cushing syndrome
     Exogenous corticosteroid or drug (liquorice) administration
     Bartter syndrome
  2. Severe hypokalemia

* U_{Cl^-} = Urinary chloride

The clinical features of metabolic alkalosis arise from the body's attempt to correct the disorder through hypoventilation. The patient may pick at her clothes (*carphology*), be confused and nauseous. Diarrhea may occur. Constipation should raise the possibility of ileus due to potassium deficiency. When alkalosis is severe, levels of ionised calcium may fall low enough to precipitate tetany.

As shown above, metabolic alkalosis may be due to volume contraction (low urinary chloride) which would be saline-responsive, or it may be due to mineralocorticoid excess (volume expansion with normal urine chloride) and would be saline non-responsive. For saline-responsive conditions, intravenous saline corrects the abnormality. If the pH is >7.55, emergent intravenous therapy with acid should be instituted. The acid deficit is calculated as the product of the base excess and 50 per cent of the body weight. The alkalosis should only be corrected halfway towards normal. Isotonic HCL through a central line (150 ml of 1.0 N HCL in 1 litre of water [130 mEq/L] at a rate of 0.2 mEq/kg/hour) or 0.1 ammonium chloride solution through a peripheral vein may be used. Metabolic alkalosis due to mineralocorticoid excess responds to therapy for the underlying disease; potassium-sparing diuretics are occasionally effective. The alkalosis of Bartter syndrome responds to prostaglandin synthesis inhibitors.

Respiratory acidosis

This is a disorder characterised by acidosis on the basis of inadequate excretion of carbon dioxide by the lungs (pH <7.35 with PCO_2 >45 mmHg). The causes are the same as those of hypercapneic respiratory failure (see section on respiratory diseases). The manifestations are those of *CO_2 narcosis*: agitation, headache, asterixis, papilledema, somnolence and cardiac arrhythmias (multifocal atrial tachycardia is typical). The treatment is that of the underlying primary disorder. It should be remembered that in these patients oxygen therapy is instituted

with great caution as the main stimulus for ventilation is hypoxemia.

Respiratory alkalosis

Respiratory alkalosis arises primarily due to increased wash-out of carbon dioxide by the lungs (pH >7.45 with PCO_2 <35 mmHg). Causes include pneumonia, panic attacks, heart failure, high altitude, pregnancy, salicylate poisoning, liver disease, gram-negative sepsis and excessive ventilation by mechanical ventilators.

Hyperventilation is the most prominent sign. The patient may complain of circumoral paresthesiae, acroparesthesiae, light-headedness, giddiness or syncope. Frank tetany may occur. Treatment consists of that of the underlying cause. When severe anxiety is the cause, rebreathing into a mask is helpful in relieving symptoms.

INHERITED DISORDERS OF METABOLISM

Inherited abnormalities of most of the important metabolic pathways in the body have been reported. These disorders are usually caused b an enzyme deficiency or a defect in a transpo protein. Some of these disorders ar incompatible with life, others present in infanc and still others may manifest only in adult life. A detailed discussion of these numerous metaboli abnormalities is beyond the scope of this tex and only a very broad overview is provided Some disorders are presented as tables and few more common ones are described. Disorder of lipid metabolism have been discussed i the section on cardiology and will not b discussed here.

Aminoacidurias and Organic Acidemias

These are a heterogeneous group of disorder which present in infancy and childhood wit mental retardation and seizures. Som important diseases are summarised in Tabl 16.22. The *aminoacidurias* are usuall characterised by developmental delay, abnorma neurologic development, or a characteristi odour of the urine. *Homocystinuria* has a mor

Table 16.22 Aminoacidurias and organic acidemias

Disease	*Inheritance*	*Enzyme deficiency*	*Stored material*	*Clinical features*
homocystinuria	AR	Cystathionine β-synthase	Homocystine (stroke)	Ectopia lentis, multiple vascular thromboses
Phenylketonuria	AR	Phenylalanine hydroxylase	Phenylalanine, phenylpyruvic acid	Mental retardation
Maple syrup urine disease	AR	Branched chain ketoacid dehydrogenase complex	Urine: branched chain ketoacid	Ketoacidosis, infantile seizures, progressive encephalopathy, characteristic odour
Methylmalonic acidemia	AR	Methyl-malonyl CoA mutase	Methylmalonic acid	Ketoacidosis, hyperammonemia
Non-ketotic hyperglycinemia	AR	Glycine clearance system	Glycine	Coma, progressive encephalopathy
Propionic acidemia	AR	Propionyl CoA carboxylase	3-hydroxypropionic acid	Ketoacidosis, hyperammonemia
Isovaleric acidemia	AR	Isovaleryl CoA dehydrogenase	Isovaleric acid	Ketoacidosis, hyperammonemia
Glutaric aciduria	AR	Glutaric CoA dehydrogenase	Glutaric acid	Progressive encephalopathy, spasticity, choreoathetosis

distinctive physical appearance (tall, long-limbed individual with an ocular lens dislocated downwards) and a tendency to vascular thrombotic episodes. The *organic acidemias* are characterised clinically by metabolic ketoacidosis, a secondary mild to moderate hyperammonemia and secondary carnitine deficiency. There may be associated developmental delay, abnormal neurologic development, hypotonia, abnormal urinary odours and protein intolerance. Some like *mevalonic aciduria* are associated with craniofacial dysmorphism.

Screening for some of these amino acid metabolic disorders (notably, phenylketonuria) is routine as part of neonatal care at several centres. Screening the urine for the amino acid or abnormal metabolite helps in the diagnosis. Confirmation can be obtained by measuring the activity of the defectives enzyme in cultured fibroblasts. With improvements in molecular biology, the genetic defects are being characterised; for instance, *maple syrup urine disease* can arise from defects in one or more of the three genes (located on three different chromosomes, 1, 6 and 19) for the deficient enzyme (branched chain ketoacid dehydrogenase complex).

Lysosomal Disorders

These disorders result from defects in one or more of lysosomal hydrolytic enzymes which results in accumulation of products which interfere with normal cellular function. Most of these disorders present fairly early in life, although some may manifest in adulthood. The disorders present with subacute neurodegeneration, organomegaly, skeletal and facial changes and macular cherry red spots (in some). Since these lysosomal enzymes are fairly widely distributed, diagnosis is easy with the help of enzyme assays in peripheral blood white cells or in cultured skin fibroblasts.

This group can be subcategorised into two groups: the *lipid storage disorders* and the *mucopolysaccharidoses.* The lipid storage disorders are associated with accumulation of abnormal lipids in various organs resulting in visceromegaly and abnormal function. Some important diseases are summarised in Table 16.23.

The mucopolysaccharidoses are a group of heterogeneous diseases due to genetic defects in enzymes degrading complex glycosaminoglycans (mucopolysaccharides). The abnormal substances are stored in various organs and include heparan sulfate, dermatan sulphate, keratan sulphate, chondroitin sulfate; some of these compounds can also be detected in urine. They carry eponyms and are inherited as autosomal recessive traits, except for *Hunter syndrome* which is inherited as an X-linked recessive trait. Clinical features include corneal clouding, abnormal facies (coarse, with thick lips), hepatosplenomegaly and joint deformities with varying degrees of mental retardation.

Disorders of Carbohydrate Metabolism

Galactosemia results from an impaired conversion of galactose to glucose (typical defect of galactose-1-phosphate uridyl transferase, less often deficiency of galactokinase) and presents with cataracts, failure to thrive, liver disease and mental retardation. *Hereditary fructose intolerance* is an autosomal recessive disorder due to a defect of the hepatic enzyme fructose-1-phosphate aldolase. It is characterised by vomiting and hypoglycemia following ingestion of food rich in fructose. These disorders are suspected by the presence of positive reducing substances in urine.

The *glycogen storage disorders* are a heterogeneous group of disorders characterised by defects in enzymes involved in glycogen metabolism either in the liver or the muscle. These disorders may manifest with hepatosplenomegaly, hypoglycemia, hyperlipidemia, lactic acidosis, macroglossia, skeletal myopathy and elevated liver transaminases or muscle enzymes. These disorders are summarised in Table 16.24.

Table 16.23 Some common lipid storage disorders

Disease	*Inheritance*	*Enzyme deficiency*	*Stored material*	*Clinical features*
Tay-Sachs	AR	Hexosaminidase A	GM_2 ganglioside	Growth retardation, progressive encephalopathy, blindness, cherry-red spot on macula, seizures, death by 2 years
Tay-Sachs variant	AR	Hexosaminidase A and B	Globoside and GM_2 ganglioside	Same as above but more rapid progression
Neimann-Pick	AR	Sphingomyelinase type A	Sphingomyelin	infantile: hepatosplenomegaly, psychomotor deterioration, cherry-red spot macula later onset: less severe disease
Gaucher	AR	β-glucocerebrosidase	Glucocerebroside	Infatile: rapid neurologic deterioration Juvenile and adult: hepatosplenomegaly, fractures, bleeding diathesis
Fabry	X-linked recessive	Ceramide trihexoside α-galactosidase	Ceramide trihexoside	Painful neuropathy, renal insufficiency, skin lesions (angiokeratomas), strokes, telangiectasia, cataracts
Globoid leukodystrophy (Krabbe's)	AR	Galactocerebrosidase	Galactocerebroside	Progressive encephalopathy, seizures, spasticity, blindness
Metachromatic leukodystrophy	AR	Arylsufatase A	Sulphatide	Progressive encephalopathy, neuropathy, ataxia, spasticity
GM_1 gangliosidosis	AR	β-galactosidase	GM_1 ganglioside	Dementia,choreoathetosis, progressive ataxia

Disorders of gluconeogenesis (such as pyruvate decarboxylase deficiency) result in difficulty in maintaining glucose homeostasis. Alternative sources of energy are mobilised, resulting in lactic acidosis, hyperalaninemia, ketosis, and sometimes, hyperammonemia. Clinically, there may be failure to thrive, growth retardation, hypotonia and seizures.

Disorders of β-oxidation

Defects in β-oxidation of fatty acids result in *hypoketotic hypoglycemia.* Clinical findings of energy depletion may be present and these include weakness, myopathy, myoglobinuria or a neuropathy. To diagnose these disorders, assays of urine organic acids, urine acyl glycines, blood levels of acylcarnitines are obtained to evaluate for an excess excretion of medium- and long chain dicarboxylic acids (relative to short chain ones).

Disorders of the urea cycle

This group includes six disorders characterised by an inability to excrete nitrogenous waste

Table 16.24 Glycogen storage diseases

Disease	*Inheritance*	*Enzyme deficiency*	*Clinical features*	*Laboratory findings/ Diagnosis*
Hepatic forms				
I (Von Gierke)	AR	Glucose-6-phosphatase	Failure to thrive, massive hepatomegaly, hypoglycemia, retinal lesions	↑ lactate, pyruvate; ↓ enzyme activity liver biopsy
III (Cori)	AR	Debranching enzyme (amylo-1,6,-glucosidase)	*Children*: massive hepatomegaly, moderate splenomegaly, growth retardation, hypoglycemia *Adults*: progressive myopathy, muscle wasting, cardiomegaly, cirrhosis,hypoglycemia	↑ SGOT\SGPT (children); ↓ enzyme activity liver biopsy
IV (Anderson)	AR	Branching enzyme (amylo-1,4-1,6-transglucosidase)	*Infants*: hepato-splenomegaly, muscle hypotonia, death by age2 years due to cirrhosis	↓ enzyme activity liver biopsy
VI (Her)	?	Hepatic phosphorylase	mild hepatomegaly, mild hypoglycemia	↓ enzyme activity liver biopsy
VIII	X-linked	Hepatic phosphorylase kinase	moderate hepatomegaly, mild hypoglycemia	↓ enzyme activity liver biopsy
Muscle forms				
II (Pompe)	AR	α-1,4-glucosidase (acid maltase)	*Infants*: floppy baby, cardiomegaly, fatal before age 1 due to cardiorespiratory failure; some have a slower progression with death by 20 years. *Adults*: muscle weakness without organomegaly	↑ CPK, ↓ enzyme activity, ↑ glycogen muscle biopsy, ↓ enzyme activity WBC ECG: large QRS complexes, short PR interval, inverted T waves
V (McArdle)	AR	Muscle phosphorylase	*Children*: Mild or no symptoms *Adults*: muscle cramps or severe muscle pain during strenuous exercise, rhabdomyolysis with myoglobinuria may occur	↑ CPK during episodes, ↓ enzyme activity, ↑ glycogen muscle biopsy; no increase in serum lactate levels in sample drawn from extremity after exercise

products. This results in severe *hyperammonemia* with respiratory alkalosis. If suspected, assays of urinary orotic acid, organic acids and plasma amino acids should be obtained.

Peroxisomal disorders

Peroxisomes are cellular organelles rich in several enzymes including catalase and oxidases. Examples of peroxisomal disorders include adrenoleukodystrophy and adrenomyeloneuropathy. When peroxisomal disorders are suspected, plasma levels of very long-chain fatty acids and phytanic acid should be assessed.

Marfan Syndrome

Marfan syndrome is a hereditary disorder of connective tissue characterised by ocular, skeletal and cardiovascular manifestations.

Marfan syndrome is transmitted as an autosomal dominant trait. The gene for the disorder has been localised to the long arm of chromosome 15. This genetic abnormality results in abnormal structure of one of the components of connective tissue, a protein called *fibrillin.* The clinical severity of Marfan syndrome varies greatly with some individuals manifesting the full-blown syndrome whereas others have just a few isolated abnormalities (the latter are said to have a '*forme fruste*' of the syndrome).

The typical patient is tall and thin; the arm span exceeds height and the foot to pubis measurement exceeds that from the pubis to crown. A typical feature is that the digits are long, thin and hyperextensible: this is known as *arachnodactyly.* The sternum is frequently deformed; both outward displacement (*pectus carinatum*) and inward displacement (*pectus excavatum*) are seen. Kyphoscoliosis is present and the legs may curve backward at the knee joints (*genu recurvatum*). Muscular hypotonia and weakness of ligaments predisposes to femoral and inguinal hernia and the hyperextensibility of joints predisposes to dislocation. The facies are long, the teeth appear crowded and the palate is high-arched. Ocular findings are very characteristic. The lens is dislocated upward (*ectopia lentis*) and the iris has a characteristic tremulousness (*iridodonesis*). A high-grade myopia is frequent.

The cardiovascular involvement, although not as apparent as the other clinical features, portends an adverse prognosis. The arterial media degenerates and weakens leading to aneurysm formation. Aneurysms of the ascending aorta are typical. There may be associated aortic regurgitation due to dilatation of the anulus. The aortic defect predisposes to aortic dissection. Interestingly, aortic dissection often occurs in the absence of aortic dilatation. Mitral valve prolapse is common.

There is no specific treatment for the primary abnormality of Marfan syndrome. A careful follow-up (usually with serial echocardiography) to detect aortic abnormalities (dilatation) is feasible. Prophylactic use of beta-blockers is recommended to retard the aortic dilatation. Prophylactic replacement of the aortic root is generally recommended when the aortic root reaches a diameter of 5.5 cm.

Ehler-Danlos Syndrome (EDS)

Ehler-Danlos syndrome is a group of inherited heterogeneous disorders of connective tissue characterised by hyperextensibility of joints and skin, easy bruisability, and poor wound-healing. At least ten different syndromes have been described with different defects in collagen biosynthesis. The disorder usually has an autosomal dominant inheritance pattern. Ophthalmologic features are often associated with blue sclerae, lens dislocation, myopia and widely spaced eyes. Some types are associated with a propensity for vascular rupture and others with a tendency for a hemorrhagic diathesis. A detailed description of individual syndromes can be obtained from advanced texts.

Pseudoxanthoma Elasticum (PXE)

Pseudoxanthoma elasticum is also an inherited group of about five disorders characterised by

ematurе dermal infiltration, laxity of flexural in creases, angioid streaks in the retina and a ndency towards arterial calcification and morrhage. The disease is usually transmitted an autosomal recessive trait.

DISORDERS OF METAL AND METALLOPROTEIN METABOLISM

Hemochromatosis

emochromatosis is a disease characterised by on overload of the liver and other extrahepatic ssues resulting in organ dysfunction. It may be genetic disorder or may occur secondary to ther diseases.

pidemiology The incidence of idiopathic emochromatosis is between 1:200 and 1:1,100 aking it one of the most common inherited isorders. The genetic form of the disorder (also alled *primary*) is inherited as an autosomal ominant trait. Men are clinically more often ffected than women (M:F=5–10:1); women also anifest the disease a decade later than men. resumably, a lower dietary iron content related to the absolute amount of food eaten) nd iron loss with menstruation account for this ex difference. The gene for idiopathic hemo-hromatosis lies in the short arm of chromosome . An increased frequency of the HLA A3 type s also seen, presumably due to linkage of the atter locus with the gene.

athogenesis, pathology and clinical features ron metabolism has been discussed in an earlier ection under iron deficiency anemia. The ormal body iron stores are about 0.2 to 2.0 rams and are located within the eticuloendothelial system (liver, spleen and one marrow). In hemochromatosis, whether enetic or secondary, body iron stores are ncreased. When body iron stores exceed 15–40 rams, clinical symptoms become evident.

The defect in genetic hemochromatosis is not ntirely clear but some putative mechanisms have been suggested. Most important of these seems to be a near doubling of the intestinal iron absorption. This enhanced absorption of iron may be related to an abnormal transferrin receptor in the duodenal mucosa or to a decreased mucosal ferritin content. This abnormality of iron absorption is compounded by the relative inability of the reticulo-endothelial system to 'handle' this increased body iron; the result is a shift of iron storage to parenchymal cells of the liver, myocardium, pancreas and other organs (which act as a 'sink' for excess iron). Furthermore, there is an increase in the pool of 'non-transferrin bound iron' and these parenchymal organs rapidly take up this pool of iron (by non-transferrin mediated uptake mechanisms). The result is an increase in serum ferritin levels along with an elevated transferrin saturation.

Secondary hemochromatosis is seen in thalassemics, patients with other types of hypoproliferative anemia who receive frequent blood transfusions,[1] alcoholic liver disease, portacaval shunts and porphyria cutanea tarda (see next section).

Iron is deposited initially within the hepatocytes (in a periportal region) and with an intracellular pericanalicular distribution in genetic hemochromatosis. In secondary hemochromatosis, in contrast, iron deposits in the hepatic reticuloendothelial cells (Kupffer cells). As the disease advances, distinction in deposition pattern between primary and secondary forms of the disease is lost. Extrahepatic sites of iron deposition include the cardiac myocytes and the conduction tissue of the heart, the pancreatic beta cells, synovium of the joints, the anterior pituitary, the basal cells of the epidermis, the eccrine sweat glands and the small blood vessels of the testes. The increased iron load of parenchymal cells presumably leads

1 Each unit of blood contains about 200 mg of iron. A patient who receives 2 units of blood per month for 2 years will receive about 10 grams of iron, overwhelming the storage capacity of the reticuloendothelial system slowly.

to progressive cellular damage (possibly due to iron-mediated free radical formation) and reparative fibrosis.

Symptoms of genetic hemochromatosis typically begin between the age of 40–60 years. Symptoms are non-specific and include abdominal pain, weakness, loss of libido, joint pains and a darkening of skin colour. Hepatomegaly is the most prominent physical sign besides a slate-grey discolouration of the skin (related to iron deposits). Eventually hepatic fibrosis results in macronodular cirrhosis with consequent portal hypertension. The cirrhotic liver serves as a nidus for the development of hepatocellular carcinoma. Hyperpigmentation of the skin and of scars is also noted and presumably arises from increased melanin deposition (rather than iron). Diabetes mellitus results from iron overload of the pancreatic beta cells; exocrine function of the pancreas remains intact. Pituitary dysfunction manifests as a loss of libido, impotence and testicular atrophy.

Cardiac iron deposition usually manifests as tachyarrhythmias and conduction system disease. A dilated cardiomyopathy results if cardiac iron deposition proceeds unabated. A deforming arthritis, similar to rheumatoid arthritis, may be seen and typically involves the second and third metacarpophalangeal joints.

Patients with secondary hemochromatosis present at a younger age. Signs of the primary disorder (usually thalassemia or sideroblastic anemia) may overshadow the manifestations of iron overload. Cardiac involvement with progressive congestive heart failure is a prominent feature.

Diagnosis Hemochromatosis is suspected in the typical middle-aged patient who has abdominal complaints, diabetes mellitus, a darkening of skin along with some joint pains. Laboratory tests may reveal only mild abnormalities of liver function and will help to confirm the diabetic state. Serum ferritin levels are elevated (usually over 500 ng/ml, often>1000 ng/ml) and the transferrin saturation is increased to above 50 per cent. A CT scan or an MRI the abdomen reveals increased hepatic densiti the attenuation coefficient indicates an iron-li substance. The findings are quite specific.[1] definitive diagnosis requires a liver biop provided the coagulation status permits. A increase in the quantitative hepatic iron conte to over 1 per cent of dry weight is diagnos (normal 10–100 µg/100 mg dry weight). Ir deposits can be confirmed with staining t specimen with Prussian blue.

Treatment Patients with genetic hemochr matosis are treated with regular lifelo phlebotomy at 3 month intervals. An init intensive phlebotomy (1 unit/1–2 weeks) may required. If cardiac complications are prese chelation therapy is added to phleboton Although the deranged liver functions, diabet cardiac dysfunction and skin pigmentati improve with phlebotomy, arthritis is not ve responsive and the risk of hepatocellu carcinoma remains unaltered. Patients w secondary hemochromatosis benefit from ir chelation therapy. Desferrioxamine (40 m kg/day) is administered, preferably as a nigh subcutaneous infusion.

Family members of patients with gene hemochromatosis must be screened for t disease so that phlebotomy treatment can considered and may be initiated befo irreversible organ damage supervenes.

Porphyria

Porphyria are a group of hereditary metabo disorders in which enzyme defects in the he biosynthetic pathway cause excess accumulation of porphyrins and porphy precursors.

Pathophysiology and clinical features He is the functional component of hemoglobin a heme-requiring enzymes (such as cytochro

[1] False-positive results are described with glycogen sto disease and use of amiodarone.

P-450 system). The structural components of heme include protoporphyrin IX (a tetrapyrrole ring) and iron. Heme production is active in developing erythrocytes and in the hepatocytes. Table 16.24 displays the steps in heme biosynthesis and the enzymes involved in the pathway. It also summarises the possible enzyme deficiencies in this pathway. Each porphyria has a specific enzyme defect and this often explains the clinical pattern of disease and the associated biochemical abnormalities. Furthermore, some patients have enzyme defects but do not manifest any symptoms unless increased hepatic production of porphyrins is induced by agents (drugs like barbiturates, alcohol or estrogens). All porphyria are autosomal dominant traits, with the exception of ALA-dehydrase deficiency and congenital erythropoietic porphyria which are transmitted as autosomal recessive traits.

The major clinical manifestations of porphyria are neurologic dysfunction and photosensitivity. If there is excess accumulation of *early* porphyrinogen precursors (δ-aminolevulinic acid [ALA], porphobilinogen [PBG] or both) the manifestations are *neuropsychiatric.* These manifest as recurrent attacks of abdominal pain, vomiting, tachycardia, hypertension, proximal paresis, paresthesia, fever, leucocytosis along with psychiatric symptoms; these attacks are presumably related at least in part to autonomic dysfunction. The urine may be red during these episodes, which typically last for a few days. These early porphyrin intermediates are water-soluble but lipid-insoluble; hence, during attacks, excess secretion of these intermediates is sought in the urine and not in the stools.

If there is an excess of the *distal* intermediates (uro-, copro- and protoporphyrins), *cutaneous* manifestations dominate the clinical picture. These are due to the photosensitising effects of porphyrins[1] deposited in the skin or circulating in the dermal vessels. Photosensitivity can manifest in one of two ways: as acute erythema of exposed skin (as in *protoporphyria*) or as increased fragility of light exposed skin, resulting in blister formation along with hypertrichosis and hyperpigmentation (as in *porphyria cutanea tarda*). Since these distal intermediates are lipid-soluble (and therefore excreted in bile), elevated levels of porphyrins are present in the stools. Since coproporhyrin is also water soluble, urine levels are also elevated.

When there is excess accumulation of both early and distal intermediates, manifestations are neurocutaneous (*hereditary coproporphyria* and *variegate porphyria*). Both stool and urine porphyrins are increased.

Structural liver damage is seen with two porphyrias: porphyria cutanea tarda and protoporphyria. Cirrhosis may develop in these patients.

Diagnosis and treatment Porphyria is suspected when there is a history of paroxysmal neuropsychiatric attacks, a positive family history, a demonstrable relation to precipitating factors, and diminution of symptoms with glucose, or carbohydrates[2] or sleep. Cutaneous porphyria is suspected when there is photosensitivity, blister formation and the concomitant presence of alcoholism or liver disease. Analysis of urine and stool porphyrins may further enable a distinction of the type of porphyria. Enzyme measurements in liver or erythrocytes is required for confirming the diagnosis and also for detecting disease in asymptomatic family members.

The treatment is summarised in Table 16.25. Briefly, attacks of neurological dysfunction respond to intravenous administration of hematin; precipitating drugs should be carefully avoided as should be 'fasting'. Photosensitivity in protoporphyria is ameliorated β-carotene and by phlebotomy (to remove iron from the liver) and by chloroquine in porphyria cutanea tarda (along with avoidance of alcohol, estrogens).

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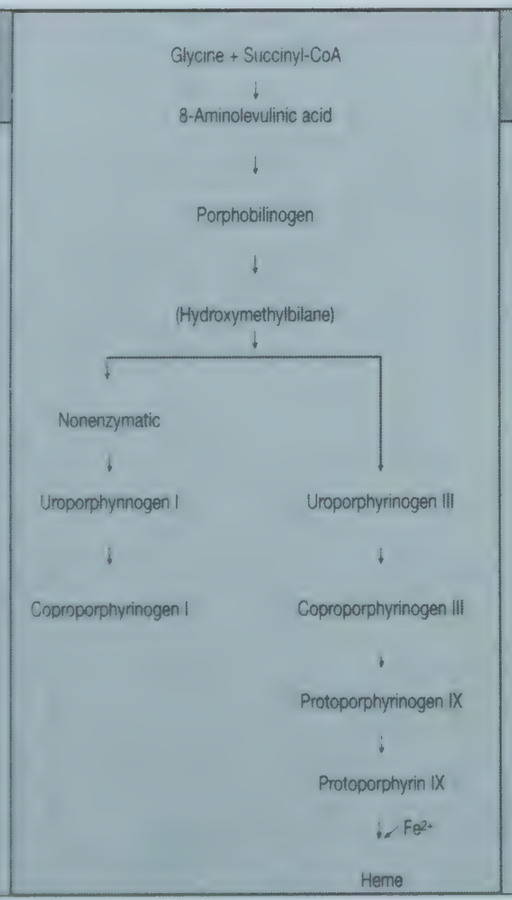
[1] It is believed that light energy excites the electrons of porphyrins resulting in the formation of singlet oxygen; the latter damages tissue membranes by lipid peroxidation and cross-linking of membrane proteins.

[2] Called the *glucose effect,* activity of hepatic ALA synthetase is decreased by these agents.

Table 16.25 Comparison of porphyric syndromes



Enzyme defect	*Disease*	*Inheritance*	*Neurologic involvement*	*Skin manifestations*	*Hepatic involvement*	*Treatment*
ALA dehydrase	ALA dehydrase deficiency	AR	+	–	–	
Porphobilinogen deaminase	Acute intermittent porphyria	AD	+	–	–	Hematin
				+		
Uroporphyrinogen III synthase (Cosynthase)	Congenital erythropoietic porphyria	AR	–	+	–	
Uroporphyrinogen decarboxylase	Porphyria cutanea tarda; Hepatoerythropoietic porphyria	AD	–	+	+	Phlebotomy, Chloroquin
Coproporphyrinogen oxidase	Hereditary coproporphyria	AD	+	+ (infrequent)	–	
Protoporphyrinogen oxidase	Variegate porphyria	AD	+	+	–	Hematin
Ferrochelatase	Portoporphyria	AD	–	+	+	Beta-carotene to reduce photosensitivity

Wilson's Disease (Hepatolenticular Degeneration)

Wilson's disease is an autosomal recessive potentially fatal but treatable disturbance of copper metabolism which is characterised by progressive liver and/or neurological dysfunction.

Pathogenesis and clinical features Wilson's disease occurs in individuals homozygous for an abnormal gene located on chromosome 13 (13q 14-q21). About 1 in 30,000 individuals are homozygous for the abnormal gene, whereas 1 in 100 people are likely to be heterozygous for the abnormal gene. Individuals with the abnormal gene have an inherited defect of hepatic lysosomes in the excretion of copper derived from the cleavage of *ceruloplasmin*[1] into bile. Consequently, hepatic levels of copper increase. The increased cellular levels of copper further inhibit the formation of ceruloplasmin from copper and *apoceruloplasmin* (a precursor compound). This sets up a cycle by which hepatic levels of copper are further elevated while plasma ceruloplasmin levels are low. Hepatic copper overload results in hepatocyte cirrhosis. This account for the *liver-related* manifestations of Wilson's disease. When hepatic capacity to store excess copper is exceeded, the copper spills over into extrahepatic tissues, notably the central nervous system. This results in the 'neurological' manifestations of Wilson's disease. Since copper deposits within the basal ganglia (particularly in the lenticular nucleus), the neurological manifestations are those of a movement disorder. During the mobilisation of copper from the liver into the central nervous system, the *Descemet's membrane* of the cornea (which has a peculiar vulnerability to copper deposition) becomes affected. The result is a golden (or golden-brown) corneal ring of copper deposits, the *Kayser-Fleischer ring.*

The accumulation of copper in the liver and the central nervous system begins at birth but clinically overt symptoms of organ dysfunction take time to evolve. Symptoms typically begin in adolescents, although the disorder can present any time from the age of 5 to 50 years. Roughly half the patients present with 'liver-related' manifestations, whereas in the other half a neurological illness draws attention to the diagnosis.

The patient may present with acute hepatitis (diagnosed as viral hepatitis) or may subsequently develop a chronic active hepatitis. Sometimes symptoms may be minimal and the patient may be undergoing investigations to evaluate a persistent unexplained transaminasemia. Occasionally, symptoms can be minimal and the patient may present with 'cryptogenic' cirrhosis. Very rarely, fulminant hepatitis may occur; the vascular release of copper in this situation usually results in a concomitant acute hemolytic episode.

The neurological illness can take one of two forms. More commonly, a *movement disorder* is seen, typically beginning in adolescence. Tremors (rest and intention types), dystonia, choreiform movements, dysarthria, drooling, varying degrees of incoordination, varying degrees of spasticity and rigidity are seen. Sensory findings are absent and suggest an alternative diagnosis. One important finding to be remembered is that neurological dysfunction does not occur without copper deposition in the Descemet's membrane; stated in another way, if a Kayser-Fleischer ring is absent in a patient with neurologic disease compatible with the diagnosis, Wilson's disease can be excluded. The second type of neurologic dysfunction presents more dramatically with *episodes of psychoses* (often suggesting schizophrenia or a manic episode), grossly inappropriate behaviour or sudden dramatic worsening in school performance. The finding of a typical corneal ring helps identify these patients.

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[2] Ceruloplasmin is a copper transport protein.

Rare manifestations of Wilson's disease include renal tubular dysfunction due to copper toxicity, and amenorrhea or repeated miscarriages in women of child-bearing age.

Diagnosis Wilson's disease is a treatable cause of hepatic and neurological dysfunction. It is therefore imperative that the diagnosis be considered in all adults below the age of 40 years who present with unexplained hepatitis or cirrhosis or with an unexplained movement disorder. A history of persistent transaminasemia in a sibling or first-degree relative also raises suspicion of Wilson's disease and must be actively sought in the history. Furthermore, since central nervous system involvement does not occur without corneal deposition of copper, a careful *slit-lamp examination* must be obtained if a Kayser-Fleischer ring is not visible to the naked eye.

The diagnostic criteria for Wilson's disease are summarised in Table 16.26. Demonstration of abnormal copper deposition (in the liver or the central nervous system) alongwith an abnormality of ceruloplasmin metabolism is important.

Treatment Untreated, Wilson's disease is fatal, usually by the age of 30 years. Treatment of Wilson's disease requires lifelong continuous administration of a copper chelating agent. The aim of therapy is to reduce serum levels of free copper to below 10 µg/dl. *D-penicillamine* is the chelating agent of choice. The drug is administered orally at a daily dose of 1 gram (divided into a morning dose on an empty stomach, and a bedtime dose at night). Monitoring of peripheral blood white cell and platelet counts is important during the initial month in order to identify drug-hypersensitivity. In cases of acute hypersensitivity, the drug should be discontinued and prednisone (20 mg/day) instituted once the granulocyte count begins to normalise. The drug may then be reinstituted at a lower dose and gradually increased over a four week period. The patient with neurologic manifestations must be counselled that transient worsening of neurologic symptoms and signs can occur during the initial phase of treatment but is no cause for concern.

During chronic therapy, additionally periodic urinalysis (to check for proteinuria) is required. If proteinuria exceeds 1–2 g/24 hours, an

Table 16.26 Criteria for diagnosis of Wilson's disease

Presence of any one of the paired criteria is enough to diagnose Wilson's disease[1]		
1. Presence of Kayser-Fleischer ring*	and	any typical neurologic abnormality described in text
2. Presence of Kayser-Fleischer ring*	and	plasma ceruloplasmin level <20 mg/dl
3. Plasma ceruloplasmin level <20 mg/dl	and	24-hour urinary copper excretion >200 µg (without D-penicillamine)
4. Plasma ceruloplasmin level <20 mg/dl	and	excess hepatic copper (>250 µg/g dry liver)
5. Low ^{64}Cu incorporation into ceruloplasmin (even if level of ceruloplasmin normal)	and	excess hepatic copper (>250 µg/g dry liver)

* detected clinically or by slit-lamp examination

[1] paired criteria are formulated as only one of the pair may be present without the subject's having Wilson's disease. For instance, heterozygote carriers of the Wilson's disease gene may have low ceruloplasmin levels but never develop the disease and, hence, do not require any treatment. Similarly, elevated hepatic copper (and even a K-F ring) may be present in primary biliary cirrhosis and some other cholestatic syndromes. The paired criteria are, however, not satisfied as plasma ceruloplasmin levels are normal.

alternative drug *trientine hydrochloride* (1 g/day in 4 divided doses before meals) should be considered. The latter drug is associated with sideroblastic anemia.

Recent reports have suggested a beneficial effect with *zinc maintenance* therapy (150 mg element per day) but the exact role of this drug needs to be further defined. It is generally recommended that patients with Wilson's disease also take pyridoxine supplements (25 mg/day). Although not strictly necessary, avoiding foods rich in copper (chocolates, nuts, meats such as 'liver' parts) may be helpful.

Examination of all asymptomatic siblings is mandatory to identify presymptomatic homozygotes.

Carcinoid Syndrome

The carcinoid syndrome is characterised by episodes of cutaneous flushing, diarrhea, abdominal cramps and bronchoconstriction, usually caused by metastatic intestinal carcinoid tumours which secrete vasoactive substances.

Pathophysiology and clinical features Carcinoids are functioning tumours of the enteroendocrine cells of the ileum. These malignant tumours produce a number of vasoactive substances, such as serotonin, histamine, bradykinin, prostaglandins and polypeptide hormones. The tumours release these substances into the hepatic portal circulation and these mediators are promptly inactivated by liver enzymes. Hence, clinical features do not occur unless the hepatic inactivating machinery is bypassed in some way. This happens when the tumour metastasises to the liver. The hepatic metastases elaborate these substances and discharge them directly into the systemic veins, thereby escaping inactivation by the liver. The tumour products then result in the clinical syndrome: paroxysms of cutaneous flushing occur, often beginning in the neck and face and soon involving other areas. Striking changes in the colour of the skin may be seen; progression may occur from pallor to erythema to a cyanotic hue. The cutaneous phenomena are probably related to release of histamine and bradykinin. There is associated abdominal cramps and diarrhea, probably due to release of serotonin. During attacks, a few patients may experience bronchoconstriction (asthma-like attacks). The cardiac structures may be involved in carcinoid syndrome, probably due to the fibrogenic actions of serotonin. Classically, the right side of the heart alone is involved and pulmonic stenosis and tricuspid regurgitation being the valvular lesions. The tumour products are inactivated by the lungs so that the left side of the heart is spared. Bronchial carcinoids bypass the lung inactivation machinery and their products can cause stenotic lesions of the left heart valves. Since the tumour diverts tryptophan into serotonin synthesis, a few patients may develop pellagra-like lesions.

Diagnosis The diagnosis of carcinoid syndrome is suspected from the typical clinical attacks. Confirmatory evidence may be sought by evaluating the urine for metabolites of the tumour. The urinary product of serotonin metabolism is 5-hydroxyindoleacetic acid (5-HIAA). The normal 24-hour excretion of 5-HIAA is less than 10 mg. Urinary levels of 5-HIAA over 50 mg/24 hours are quite typical of carcinoid tumours.[1] Provocative tests (using alcohol, pentagastrin, etc.) have been described but are rarely used. A liver scan may demonstrate metastases.

Treatment Surgical resection is rarely feasible in carcinoids, except for localised primary lung carcinoids. Despite the malignant nature of the tumour, survival of patients for 10–15 years is usual. Chemotherapy with streptozocin and

1 The patient must avoid serotonin-containing food (such as bananas, walnuts, tomatoes, brinjals and plums) for 3 days to avoid false-positive results.

5-fluorouracil has been attempted for metastatic disease. The somatostatin analogue, octreotide, has also been reported to be effective.

Treatment of the paroxysms depends on the predominant manifestation. Diarrhea responds to codeine, peripheral serotonin antagonists (cyproheptadine 4–8 mg q 6 h), or to enzyme inhibitors which prevent the conversion of tryptophan to serotonin (methyldopa 250 mg q 6 h or phenoxy benzamine 10 mg/d). Cutaneous flushing responds to phenothiazine or H_2 receptor antagonists (cimetidine). Corticosteroids may be helpful in relieving bronchoconstriction.

KEY CONCEPTS

Hereditary hemochromatosis

- Herditary hemochromatosis is an autosomal recessive disorder (gene on the long arm of chromosome 6) characterised by parenchymal iron overload and dysfunction.
- The basic abnormality is excessive absorption of iron. Women are relatively protected from the disorder due to menstrual loss of blood.
- The liver, pancreas, skin, pituitary gland, the synovium of the joints and the heart are sites of iron deposition. This results in hepatic cirrhosis, diabetes mellitus, bronze discolouration, hypopituitarism, arthritis, and cardiomyopathy.
- Increased plasma levels of iron (>200 μg/dl), serum ferritin (>1000 ng/ml) and an increased transferrin saturation (>50%) suggest the diagnosis. The CT scan appearance of the liver is corroborative and the presence of excess iron on biopsy (>1% dry weight) is diagnostic.
- Treatment consists of repeated phlebotomy (500 ml weekly until serum iron normalises, followed by once every 3 months) to maintain serum iron <150 μg/dl.

Porphyria

- This is a rare group of inherited/acquired disorders in heme biosynthetic pathways in erythrocytes (erythropoietic porphyria), hepatocytes (hepatic porphyria) or both (erythrohepatic porphyria), which result in the accumulation of toxic intermediates; accumulation of early heme precursors (ALA, PBG) results in neuropsychiatric manifestations while excess of distal intermediates (uro-, copro- and protoporphyrins) causes cutaneous manifestations (acute erythema, chronic blistering and hypertrichosis).
- Acute intermittent porphyria is the most severe acute form. Young adults are affected and present with abdominal pain, a variable degree of motor paresis, and autonomic dysfunction. Diagnosis is by elevated urine ALA/PBG in acute stage, and by estimating RBC deaminase in the interim phase. Acute attacks are treated with analgesia, i.v. dextrose and i.v. hematin.
- Porphyria cutanea tarda is the most common type of porphyria and is characterised by skin lesions, increased hepatic enzymes and elevated levels of urinary coproporphyrins and fecal protoporphyrins. Treatment is with phlebotomy, chloroquine and desferrioxamine.

Wilson's disease

- Wilson's disease is an autosomal recessive disease characterised by low plasma ceruloplasmin level and copper accumulation in the liver, and sometimes, the CNS.
- The disease often has an onset in childhood. It presents as an acute hepatitis or a chronic active hepatitis. Eventually hepatic cirrhosis develops.
- Neurologic manifestations occur typically in adolescence and take the form of either a movement disorder or psychosis. Involvement of the cornea with a golden-brown Kayser-Fleischer ring is pathognomonic. Renal involvement may result in tubular dysfunction.
- Key investigations for establishing a diagnosis include slit lamp examination (for KF ring), serum ceruloplasmin levels and liver biopsy assay for copper.
- Treatment consists of copper chelating agents (d-penicillamine) and, in advanced cases, liver transplantation.

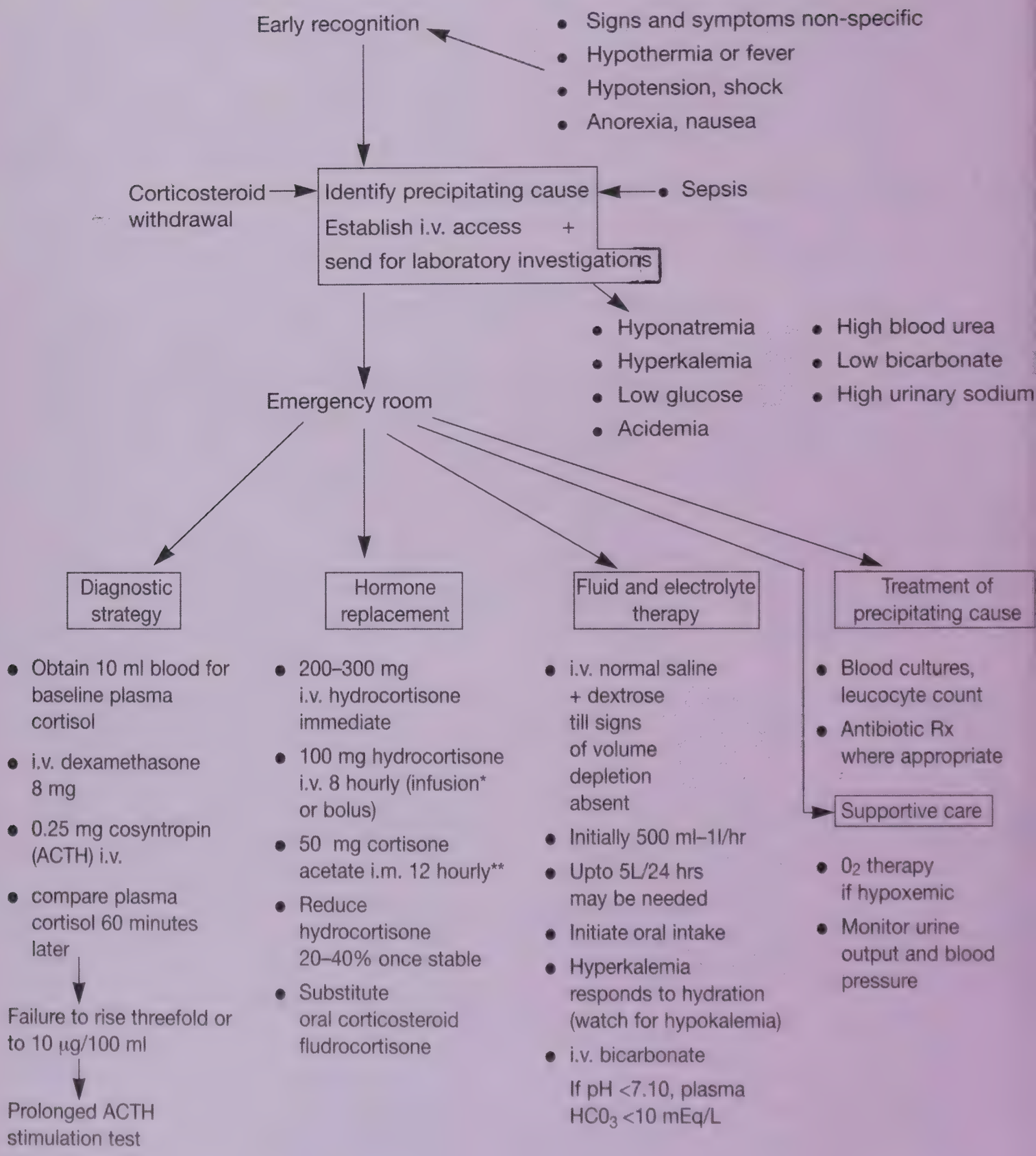
16.11 Endocrine emergencies

1. Management of diabetic ketoacidosis

Confirm diagnosis
History, clinical exam: dehydration, acidotic breathing
Lab parameters: arterial pH <7.3, blood glucose>250 mg/dL, S. bicarbonate <15mEq/L, Urine ketones +

- **Intravenous fluids**
  - 20 ml/kg body weight normal saline in first hour
    - reassess degree of dehydration (hourly BP, urine output, skin turgor)
      - **Severe/moderate dehydration**
        - Continue fluids at 10–20 ml/kg/hr; reasses hourly
      - **Mild dehydration** or **Dehydration corrected**
        - Fluids at maintenence rate 2.5–5 ml/kg/hr till oral intake commenced
          - Oral intake commenced
            - Regular meals, s.c. regular insulin before meals
- **Insulin**
  - 0.1 u/kg/hr as continuous i.v. infusion or hourly s.c injections
    - Check hourly blood glucose
      - If glucose falls below 50–75 mg/dL per hour double insulin rate
        - **Blood glucose >200 mg/dL**
          - Continue normal saline as i.v. fluid
        - **Blood glucose <200 mg/dL**
          - Change i.v. fluid to 5% dextrose
      - Continue insulin infusion till acidosis, ketonemia cleared; then commence oral intake
- **Serum K^+**
  - Check 2 hourly
    - **>5 mEq/L**
      - No K to i.v. fluid
    - **<5 mEq/L**
      - Add 20 mEq/L to i.v. fluid

2. Management of acute adrenal crisis



* Infusion preferable as the half-life of an i.v. bolus is less than 60 minutes

** Prevents abrupt discontinuation in the event of i.v. malfunction

3. Management of thyroid storm

Prompt recognition

known thyrotoxicosis with
- temperature>100°F
- tachycardia out of proportion to fever
- dysfunction of CNS, GIT
- heart failure with atrial fibrillation

- Infections
- I^{131} treatment
- Surgery
- Other causes

- Identify precipitating cause,
- establish intravenous access + nasogastric tube + laboratory investigations

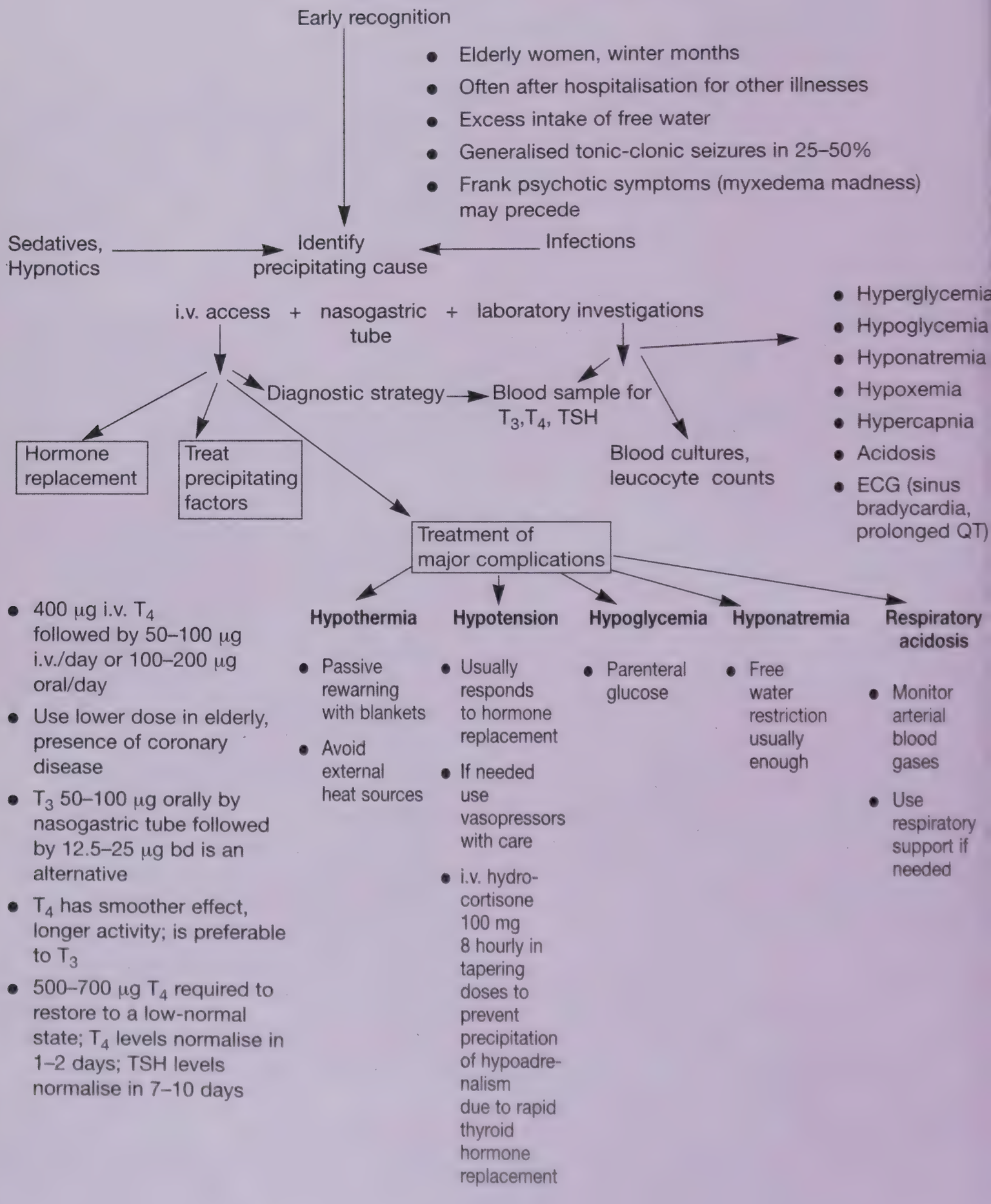
blood for T_3, T_4, TSH

- Hyperglycemia
- Hypercalcemia
- Hypokalemia
- Relative lymphocytosis with neutropenia

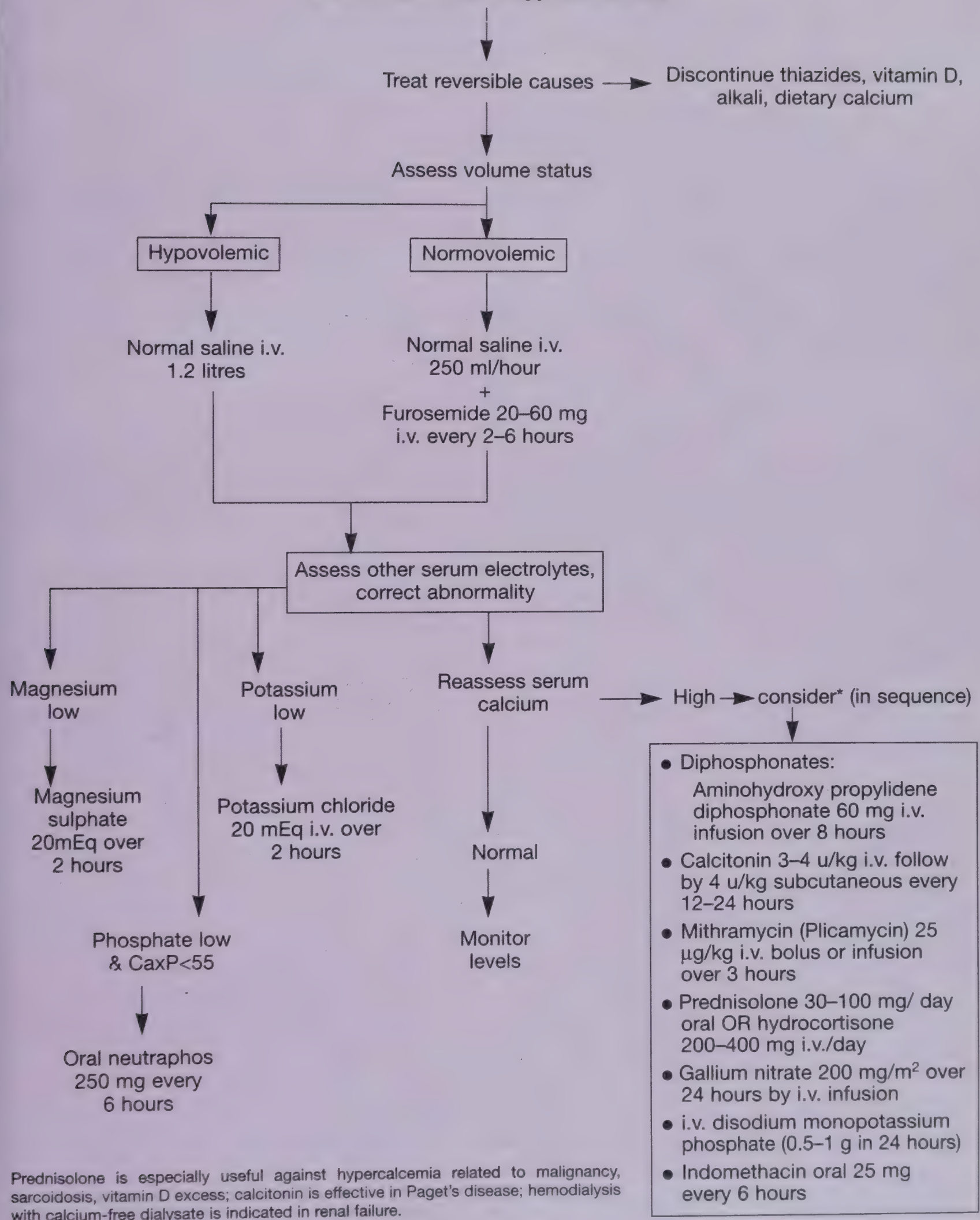
Inhibition of hormonal biosynthesis	Blockade of hormone release	Antagonism of peripheral effects	Supportive care

Propylthiouracil 400 mg every 6 hours by oral/nasogastric tube	Several alternatives
	• Sodium iodide 1 gram i.v. over 30 minutes or 250 mg oral every 6 hours
	• Saturated solution potassium iodide (SSKI) 5 drops oral every 4 hours
	• Lugol's iodine 30 drops per day
		Propranolol
		• Oral 40 mg every 4–6 hours
		• Intravenous 1 mg every 4 hours slowly
			• Hydration
			• Lower temperature
			  • External cooling
			  • Paracetamol
			  • Avoid salicylates (can↑ free thyroid hormone)
			• Hydrocortisone 50–100 mg intravenous every 6 hours

4. Management of myxedema coma

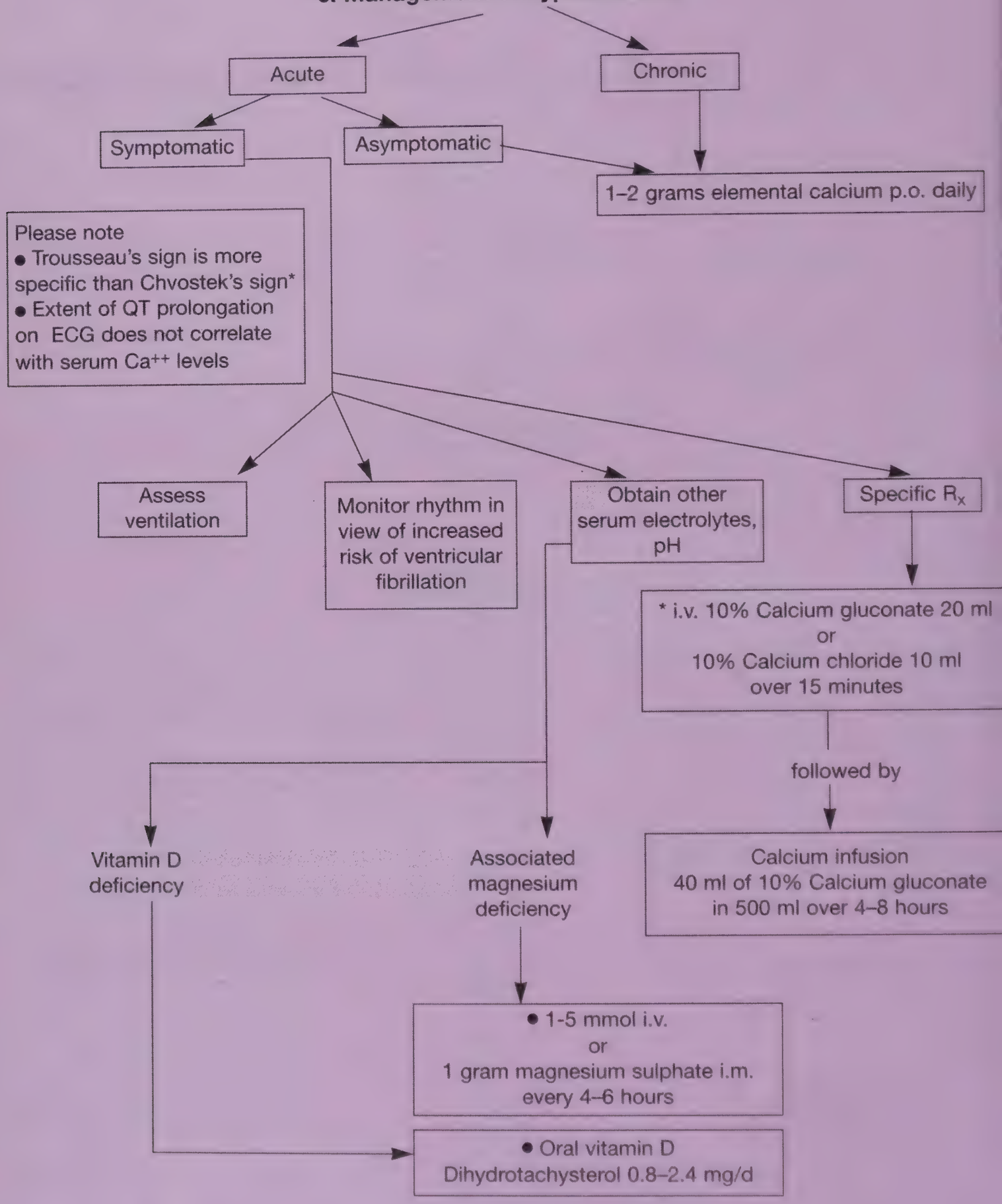


5. Management of hypercalcemia



* Prednisolone is especially useful against hypercalcemia related to malignancy, sarcoidosis, vitamin D excess; calcitonin is effective in Paget's disease; hemodialysis with calcium-free dialysate is indicated in renal failure.

6. Management of hypocalcemia



* Chvostek's sign may be present in upto 15 per cent of normal people

17

Disorders of Immune Function and Connective Tissues

17.1 Principles of clinical immunology

Immunoglobulins

Antibodies or immunoglobulins are a family of structurally related glycoproteins produced by B lymphocytes that migrate in an electrophoretic field within the slowest of the three peaks (γ peak, hence the name 'gamma' globulins). All immunoglobulins have a similar core structure of two identical light chains and two identical heavy chains linked by covalent disulphide bonds. Each light chain overlaps the amino terminal of one heavy chain and the carboxy terminal ends of the heavy chains overlap each other. The region of the overlap of the heavy and light chains is called the *F_{ab} region*[1] and the region of overlap between the two heavy and light chains is designated the *F_C region.*[2] The N terminal domains of both the light and heavy chains in the F_{ab} segment contain the *variable (V) regions,* each chain containing three separate hypervariable regions of about ten amino acids which are spatially assembled to form the 'antigen binding site' of the immunoglobulin molecule. Each light chain contains one *constant 'C' region* domain and each heavy chain contains three or four C region domains (Fig 17.1). Most of the effector functions of the antibodies are mediated by the C domains of the heavy chain. This is, of course, triggered by binding of the antigen to the V region. The F_C region thus determines how the antibody binds to complement, phagocytes and mast cells.

The heavy chain (mol. wt. 50,000–75,000) exists in five forms based on the amino acid sequence at the carboxy terminal end (γ, α, μ, δ and ε). The antibody's *isotype* is, therefore, determined by the particular class of heavy chain present; IgG antibody contains γ heavy chains, IgM contains μ chains, IgA contains α, IgD contains δ chains and IgE contains ε chains.

The light chain (mol. wt. 23,000) is one of two designated classes κ or γ. Individual antibody molecules may contain either κ or γ light chains but not both and these chains may be associated with heavy chains of any class.

Of the immunoglobulins, IgM is mostly found intravascularly, IgG is found equally in intravascular and extravascular fluids, and IgA is found in the intravascular compartment, in secretions and on mucosal surfaces. IgM is the first antibody formed after exposure to a new antigen (primary immunisation). It exists in a monomeric or pentameric form and serves as a powerful agglutinator due to its ability to promptly activate complement. IgG is the major antibody produced after reimmunisation (the memory response or secondary immune response). It is the most prevalent of all the antibodies and is the only one that crosses the placenta. IgA maintains mucosal immunity and

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1 Fraction antibody binding

2 Fraction 'crystallisable'

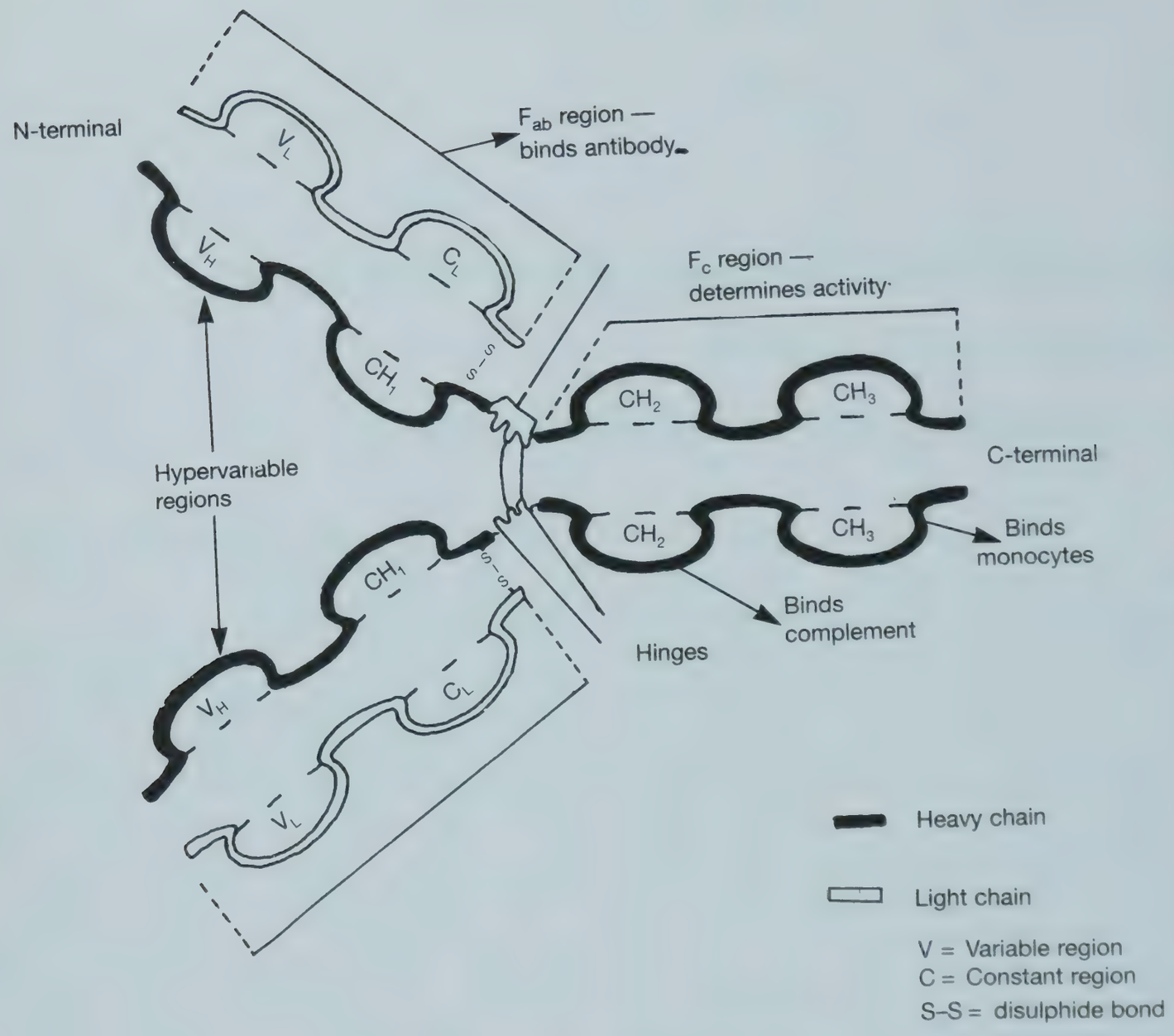


Fig 17.1 The structure of immunoglobulins

IgE has a beneficial role in defence against parasites. The biologic activity of IgD is not known.

The three-dimensional structure of the antibody molecule at the antigen binding site is the *idiotype* of the antibody. All antibodies produced by a single lymphocyte and its daughter cells (clone) express a single idiotype and are said to be *monoclonal.*[1]

[1] Monoclonal antibodies are commercially produced by a *hybridoma technique.* The splenic cells of a mouse (immunised with an antigen) are fused with a myeloma cell line and reinjected into mouse peritoneum, and the monoclonal antibody is harvested from the ascitic fluid.

Though a single B lymphocyte can change th class of heavy chain it produces, thereb changing the *isotype* of the antibody, it canno change the *idiotype.*

Lymphocytes

All lymphocytes are derived from the sam primordial stem cell with further differentiatio under the influence of varying signals into 'smal (8–10 μm) lymphocytes or 'large' granula lymphocytes (also called the 'natural' kille cells).

Two distinct populations of small lympho cytes are readily identified. The *B lymphocyte*

so called because in birds they were first shown o mature in an organ called the *bursa of Fabricius*) are bone marrow-derived cells which arry out antibody synthesis and with ppropriate stimulation can differentiate into plasma' cells. The B lymphocytes are normally rranged in the peripheral white pulp of the pleen and the outer region of the cortex of the ymph nodes, where they form 'germinal' centres nd 'secondary follicles'. These B cells are dentified by the presence of surface immuno-globulins, surface receptors for complement (resulting in rosette formation with antibody and complement coated on erythrocytes), surface receptor for the F_c fragment of immuno-globulins and directly by use of anti-B cell serum.

The *T lymphocytes* are so called as they are thymus-derived, that is, they develop under the regulation of hormone-like substances released by the thymic epithelial cells.[1] These cells are arranged in the periarteriolar lymphocyte cuff of the splenic white pulp and in the inner cortical and paracortical areas of the lymph node. T lymphocytes are identified by their ability to form rosettes with sheep erythrocytes or by specific anti-T cell serum.

All T lymphocytes carry a surface receptor for the antigen– the 'T cell receptor' (TCR).

A subpopulation of T-lymphocytes recognises certain areas of the antigenic molecule which are different from the areas recognised by the antibody. Recognition of these areas (or antigenic determinants as they are called) is termed *carrier recognition* and this results in the release of stimulating factors which promote B lymphocytes to produce antibodies. This phenomenon is called T cell help and the responsible subpopulation is called *T helper cells* (T_H). Another subpopulation of cells produces factors which depress the immune response of B lymphocytes. These T cells are called *T-suppressor cells* (T_S). The normal ratio of T_H/T_S cells is greater than one, reflecting a dominant influence of stimulatory factors. A third subpopulation of T cells lyses cells that contain foreign antigens-the *T cytotoxic cells*. These subpopulations are differentiated by the presence of functionally distinct membrane proteins. Thus, most helper T cells express a surface protein called 'CD_4'[2] and most cytotoxic and suppressor cells express a different marker called 'CD_8'. Both helper and cytotoxic T lymphocytes recognise foreign peptide antigens only if they are expressed on the surface of a cell in association with certain other proteins encoded by the major histocompatibility complex (MHC, see below).

The *natural killer cells* are large granular lymphocytes which have the ability to kill certain tumour cells and to destroy normal cells infected by viruses. They lack a 'T cell receptor' and can lyse the cells without the prerequisite that the antigen be surface bound in association with MHC molecules.

Major Histocompatibility Complex and Immune Responses

The major histocompatibility complex (MHC) is a region of highly polymorphic genes located on the short arm of chromosome 6. The antigens coded by these genes were first recognised on the surface of human leukocytes (human leukocyte antigens) and therefore the region is also called the HLA region. The MHC occupies an area of around four million base pairs and each individual has two alleles at each gene locus, both of which are expressed independently. Children usually inherit one entire set of MHC genes from each parent. Each parental set of genes is refered to as a haplotype.

The MHC region contains at least three different regions. The class I region contains genes encoding the Class I antigens HLA-A,B,C- and the Class II region contains genes

1 T cells learn the concept of self in the thymus. Autoreactive clones of T cells are eliminated.

2 CD refers to 'cluster of differentiation', that is, a molecule on the lymphocyte recognised by a cluster of monoclonal antibodies which can be used to differentiate one subpopulation from another.

encoding the class II molecules - D HLA II subregions DR, DP and DQ. The Class III region is interposed between these two genes and contains the genes for certain complement components and the gene for the 'tumour necrosis factor'.

The molecules coded by the respective MHC genes are called Class I and Class II MHC molecules and are essentially transmembrane glycoproteins. Class I molecules are expressed on the cell surface of most nucleated cells and Class II molecules are expressed on cells of the immune system which process and present foreign antigens to T cells (the antigen presenting cells, that is, the macrophages, B cells and dendritic cells). Class I molecules consist of a 45 kd transmembrane α chain non-covalently bound to β_2 microglobulin, whereas Class II molecules comprise a pair of non-covalently bound transmembrane chains, the 32kd α chain and the 28 kd $\alpha\beta$ chain (Fig 17.2).

The major function of class I and class II MHC molecules is to present the foreign antigen to T lymphocytes. The term *'MHC restriction'* is used to describe the phenomenon wherein an antigen-presenting cell must express MHC molecules which the T cell recognises in order that the T cell can recognise and respond to a foreign protein antigen. The recognition of an antigen as 'foreign' is thus the result of the *trimolecular* interaction between the MHC molecule, the antigen and the T cell receptor. The MHC molecule is recognised by the CD protein expressed on the surface of the T lymphocyte. The T helper cell expresses the CD_4 molecule which interacts with Class II MHC molecules while the T cytotoxic cell expresses the CD_8 molecule which interacts with Class I MHC molecules (Fig 17.3). It is, therefore, easy to understand that the patterns of antigen association with Class I or Class II MHC molecules will determine the kind of T cell that will be stimulated. Class II associated peptides are derived from extracellular microbes and soluble protein antigens and trigger off the T helper cells (CD_4). Class I-associated peptides are generally derived endogenously in the cell (for instance, viral antigens) and they trigger off the T cytotoxic cells (CD_8^+). Such interaction is of clincial relevance in disease pathogenesis. Thus, an interaction of CD_4^+ cells with Class II MHC genes is important in the pathogenesis of rheumatoid arthritis while a CD_8^+ T cell-Class I MHC interaction plays an importannt role in the pathogenesis of Reiter syndrome. Defects of Class III MHC genes (genes for complement components C_2 and C_4 and tumour necrosis factor) are associated with a propensity for systemic lupus erythematosus.

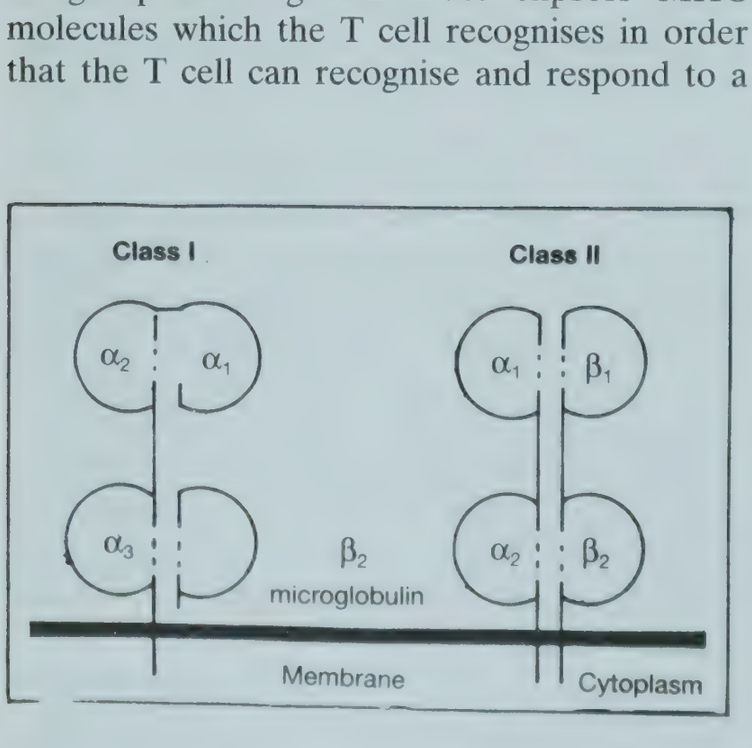


Fig 17.2 Class I and class II MHC molecules

Macrophages

Macrophages are phagocytic mononuclear cells which are derived from a hemopoietic stem cell distinct from the prelymphoid cell. In the blood these cells are called *monocytes* and when they migrate into the tissues they are referred to as *histiocytes*. Macrophages ingest particulate antigens, digest them into smaller fragments and then present the 'processed' antigen to the lymphocytes. Antigen processing greatly amplifies the immune response.

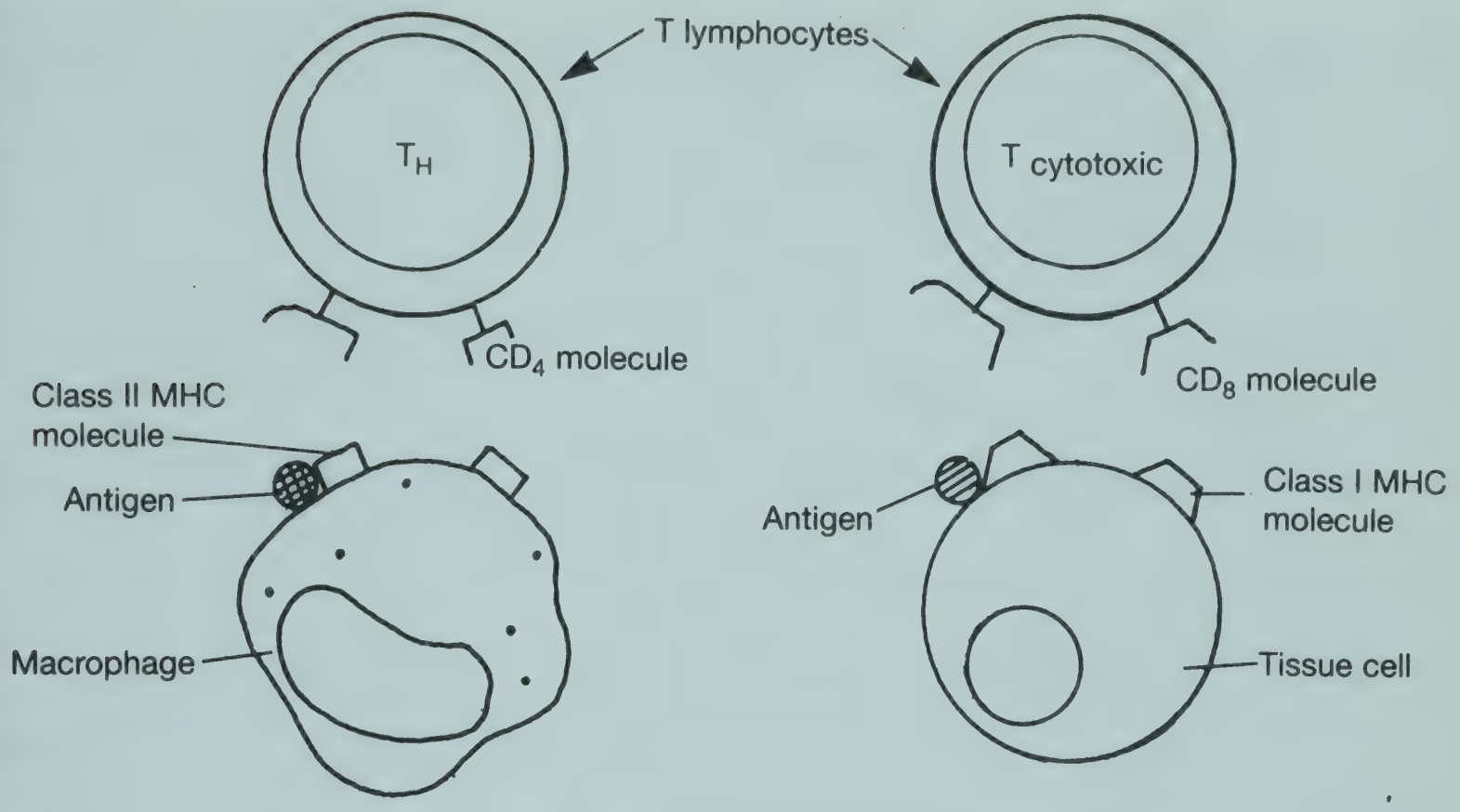


Fig 17.3 Patterns of antigen association

Complement

The complement system includes a family of about 30 serum and membrane proteins which interact in a highly regulated manner (cascade) to produce biologically active protein products. The system comprises two convergent proteolytic pathways— a 'classic' pathway and an 'alternate' pathway both composed of different *zymogens.*[1] (Fig 17.4). The classical pathway is triggered by antigen-antibody complexes and the alternative pathway is initiated in the absence of antibodies, directly by the surfaces of the microorganisms. Both pathways converge onto a common terminal pathway leading to the formation of a protein complex called the *membrane attack complex* (MAC) which punches pores in the plasma membrane of the microorganisms. Apart from cytolysis, the other biologic functions of the complement system include opsonisation of organisms and immune complexes for phagocytosis (C_{3b}), production of inflammation (anaphylatoxins C_{3a},C_{4a},C_{5a}), and solubilisation and clearance of immune complexes (C_{3b}). Deficiencies of early components (C_1 C_2 C_3) predispose to autoimmune disorders and deficiencies of late complement components predispose to disseminated infections with encapsulated organisms like *Neisseria.*

[1] Proteins that acquire proteolytic enzymatic activity by the action of other proteases are called zymogens.

Cytokines

Cytokine is a generic term applied to substances secreted by cells that influence the behaviour (in relation to immunity) of other cells. Thus *lymphokines* are products of stimulated lymphocytes which influence the behaviour of other cells. *Monokines* are products of mononuclear phagocytes (macrophages and monocytes) which influence the behaviour of other cells. *Interleukin* is the term applied to well-defined lymphokines and monokines which influence the behaviour of other leukocytes (hence interleukin). Table 17.1 depicts some cytokines with their cells of origin and biologic

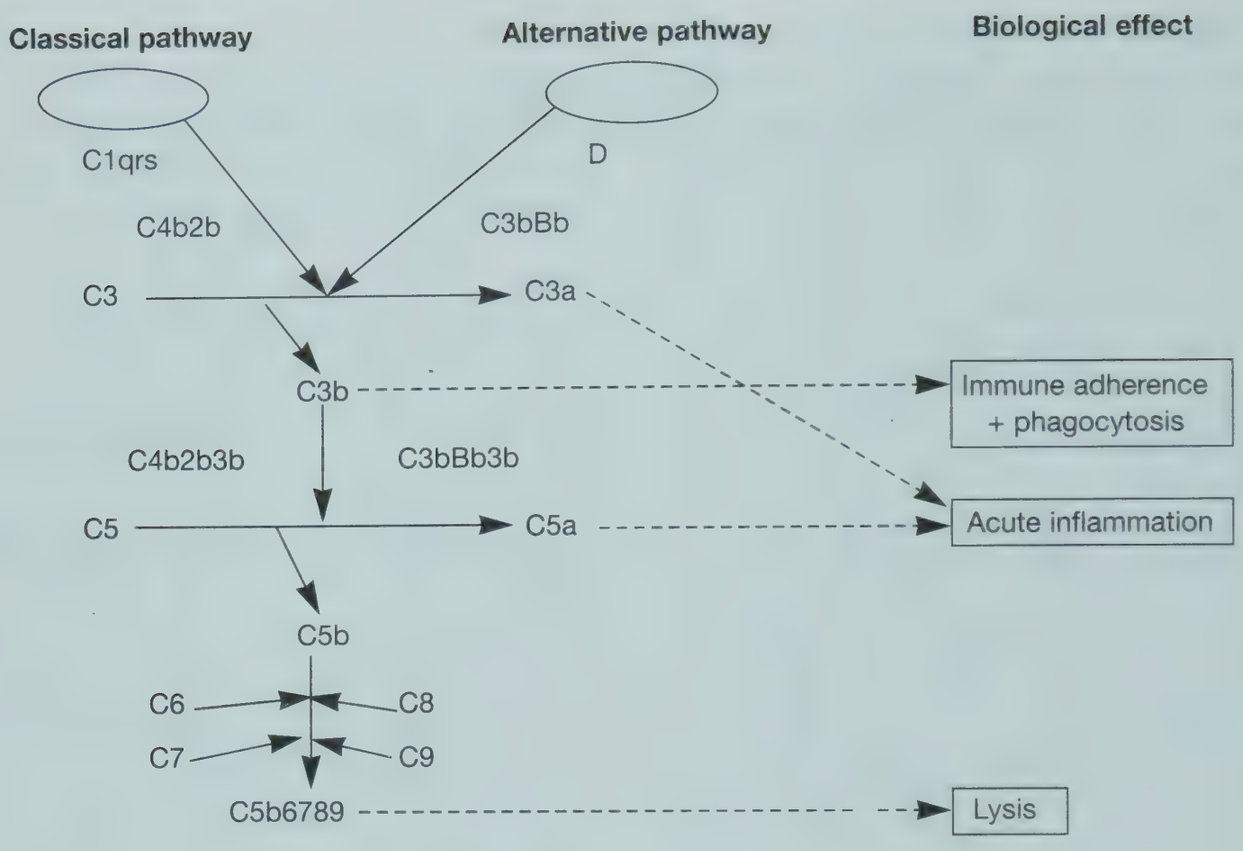


Fig 17.4 Complement pathway

effects. All cytokines share some common features. They are glycoproteins active at very low concentrations (10^{9}–10^{12} mmol/l), react with specific receptors and are not rigidly species-specific. There is often molecular heterogeneity in a well-defined cytokine due to differences in glycosylation or due to polymerisation. Apart from their central role in the induction of both cellular and humoral immune responses, cytokines are intimately involved in inflammatory diseases and proliferative diseases of blood elements and lymphoid tissues.

For the sake of simplicity, four groups of cytokines are recognised. The first group includes those cytokines which mediate natural immunity, and their predominant cellular source is the mononuclear phagocyte. These include the antiviral Type I interferons and the proinflammatory cytokines– the tumour necrosis factor (TNF), interleukin 1, interleukin 6 and members of the newly described family of low molecular weight inflammatory cytokines (interleukin 8). A second group of cytokines derived from antigen-stimulated, CD_4^+ lymphocytes and includes interleukin 2 (th principal T cell growth factor), interleukin 4 (th major regulator of IgE synthesis) an transforming growth factor β which inhibi lymphocyte responses. The third group produced by antigen activated CD_4^+ and CD_8 T lymphocytes and includes γ interfero (principal activator of mononuclear phagocytes interleukin 5 (an activator of eosinophils and lymphotoxins (an activator of neutrophils The fourth group, collectively called colony stimulating factors, consists of mediators derive from both T cells and non-specific effector cel which stimulate the bone marrow cell Interleukins 3 and 7 belong to this group.

Adhesion molecules

Immune activation also includes the appearanc of certain surface molecules termed *'adhesio molecules'* that promote adhesion to an interaction with related molecules on the surfac

Table 17.1 Classification of cytokines

Cytokine	*Source*	*Function*
Group 1: Cytokines mediating natural immunity (of predominant macrophage origin)		
IL-1	Macrophage	acute phase reactant, pyrogen, stimulates T cells, increases IL-2 levels
IL-6	Macrophage/T cell	stimulates T cells and growth of B-cells
IL-8	Macrophage	neutrophil chemotactic agent
IL-12	Macrophage	activates T cells and NK cells
TNF-α	Macrophage/T cell/NK cells	activates neutrophils; pyrogen, antitumour activity
Interferon-α/β	Macrophage	induces antiviral state, activates NK cells
Group 2: Cytokines produced by activated CD_4^+ T cells		
IL-2	T cell	proliferation of T cells, amplifies antibody synthesis, activates NK cells, anti-tumour activity*
IL-4	T cell	B cell proliferation and differentiation (Ig E isotype switch)
TGF-β	T cell/macrophage	inhibits T cell growth and macrophage activation
Group 3: Cytokines produced by activated CD_4^+ and CD_8^+ T cells		
IL-5	T cell	induces differentiation of B cells, activates eosinophils
Interferon-γ	T cell/NK cells	activates lymphoid cells, macrophages; increases HLA Class II expression with increased antigenic presentation
Group 4: Colony stimulating factors		
IL-3	T cell	growth and differentiation of bone marrow precursors
IL-7	Stromal cells of spleen	growth factor for early B and T lymphocytes
GM-CSF	Fibroblasts	stimulates growth of macrophages and neutrophils

IL = interleukin, NK = natural killer cells, TNF = tumour necrosis factor, TGF = transforming growth factor, GM-CSF = granulocyte-macrophage colony stimulating factor (sargramostim).
* recently approved for use as a therapeutic agent in metastatic renal carcinoma

of other activated cells. The role of the adhesion molecules is particularly striking in the phenomenon of neutrophil adhesion to vascular endothelium and their emigration into the tissues (diapedesis). The neutrophils initially roll over the endothelium drawn by the chemotactic mediators. This loose adhesion is facilitated by the interaction of transmembrane glycoprotein called selectins, on the surface of the neutrophil (L-selectin) and the vascular endothelial cell (E-selectin or formerly called ELAM, that is endothelial leucocyte adhesion molecule). This initial interaction is followed by the stronger adhesion or tethering of the neutrophils to the

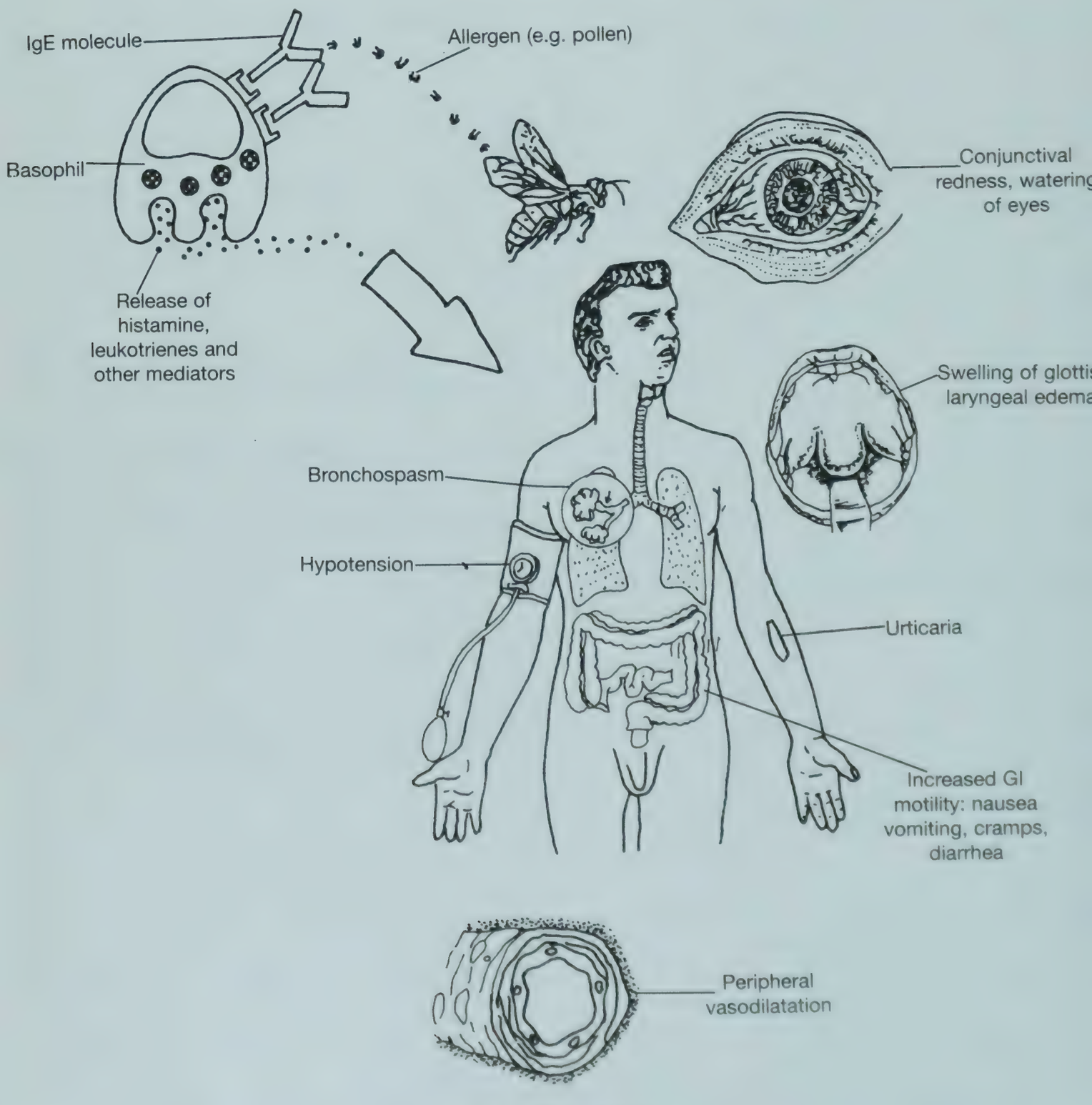


Fig 17.5 Type 1 reaction

ndothelium, in part stimulated by the release of ytokines from the activated endothelial cells. his step involves the interaction of the olecules (called integrins) on the neutrophil urface (LFA-1, Mac-1) with ICAM intercellular adhesion molecules) on the ndothelial surface. Likewise the binding of omplement components to phagocytes is acilitated by the CR_4 molecule (complement eceptor 4). Deficiency of adhesion molecules an result in clinical disease. Thus, infants with eucocyte adhesion deficiency (defect in gene on hromosome 21 resulting in deficiency of LFA) ave some delayed loss of the umbilical stump, severe periodontitis and severe soft tissue nfections without pus formation.

Mechanisms of immunologic injury

Coombs and Gell in the early 1960s had proposed a classification of mechanisms of 'immunologic' injury that remains fundamental to understanding the pathophysiology of immune diseases.

Type I or immediate hypersenstivity reaction This category includes immune reactions to pollen, dust, food and some drugs, penicillin being a typical example. The Fc portions of IgE molecules bind avidly to basophils and mast cells. When this cell-bound IgE encounters the specific antigen, cross-linking of molecules (bridging) results and this triggers the release of several preformed mediators as well as that of newly formed mediators: the result is an 'anaphylactic' reaction. The preformed mediators include histamine, serotonin, eosinophil and neutrophil chemotactic factors. The newly generated mediators include the platelet activating factor, kinins (e.g., bradykinin), prostaglandins and a mixture of leukotrienes (formerly called 'slow reacting' substance of anaphylaxis).

The clinical picture is characterised by life threatening events occurring over seconds to minutes. There may be skin reactions varying from erythema or pruritus to urticaria. The upper respiratory tract is involved with glottic and laryngeal edema of varying severity along with rhinorrhea. Release of several vasodilatory mediators results in hypotension and cardiovascular collapse (Fig 17.5).

The steps in the treatment of anaphylaxis include the immediate administration of 0.5 ml of a 1:1000 solution of epinephrine subcutaneously along with an appropriate dose of H1 receptor antagonists (diphenhydramine, 25–50 mg i.m. or slow i.v.). The second generation of H1 receptor antagonists (terfenadine or loratidine) are increasingly being preferred, where available, because of a relative lack of side effects (such as sedation) compared to the first generation agents. H2 receptor antagonists may also be useful as adjuncts because about 15% of vascular histamine receptors are of the H2 type. Intravenous fluids (saline, Ringer's lactate) are administered to maintain intravascular volume. Airway obstruction also requires prompt attention. Endotracheal intubation may be necessary. A laryngeal obstruction may necessitate tracheostomy. Bronchoconstriction can be treated with intravenous beta-2 agonists (terbutaline).

Type II (cytotoxic antibody) reactions This category includes at least three types of reactions: 1) complement-mediated lysis: In this reaction, IgM or IgG antibodies directed against cellular surface antigens activate complement and thereby result in cytolysis. An example of this is transfusion reaction (with hemolysis of erythrocytes). 2) Antibody-dependent cell-mediated cytotoxicity: In this category, cytotoxic cells recognise the F_c portion of target bound antibodies, thereby resulting in cell lysis, for instance, immune response to helminthic infection. 3) Antibody-induced cellular dysfunction: In this category, antibodies to cell surface receptors cause cellular dysfunction, for example, antibodies to acetylcholine receptors in myasthenia gravis.

Type III (immune complex) reactions In this category, intermediate-sized immune complexes deposit in tissues and on endothelial surfaces, activate complement and thereby mediate tissue injury. The classic example is serum sickness (reaction to heterologous serum or drugs like penicillin). The manifestations depend on the tissues injured: blood vessels (vasculitis), glomeruli (glomerulonephritis), joints (arthritis) and skin (dermatitis). Complement consumption results in serologic evidence of hypocomplementemia.

Type IV immune response (cell-mediated immunity) In this type of immune response (also called delayed type hypersensitivity), tissue damage is caused by cells and not by antibodies. Cellular immune responses (CMI) are generally slower than humoral responses, and the affected tissue is infiltrated by lymphocytes and macrophages (in contrast to the polymorphonuclear infiltrate in the Arthus reaction). CMI responses can be potentially transferred to an unprimed animal by injection of T cells but not by injection of serum. Lymphocytes play a central role in CMI and release lymphokines which recruit the non-specific effector cells—the macrophages. The macrophages transform into epitheloid cells and giant cells may be seen in the tissues; this tissue response is also called *granulomatous inflammation*. Skin tests with sensitising agents like di-nitrochlorobenzene are associated with response after 48-72 hours and are used to assess integrity of CMI responses. CMI is especially important in combating intracellular microorganisms (such as the tubercle and lepra bacilli, fungi, Listeria), toxins (beryllium) and organic dusts (hypersensitivity pneumonitis). Allograft rejection, contact dermatitis, the Mantoux test are some more clinical examples involving CMI (delayed hypersensitivity responses).

Mechanisms of autoimmune disease

Autoimmune disease are characterised by the presence of autoantibodies in the sera of affected patients. Autoantibodies can mediate the clinical effects in several diseases (as in myasthenia gravis). Nonetheless, these antibodies may also simply be an epiphenomenon of what is essentially a T cell dependent effect. Normally, the immune system is tolerant to the self antigens because of the removal of autoreactive clones of T cells. Yet under certain circumstances, this self-tolerance may break down and autoreactive T cells can mediate a destructive response on tissues. There are several models of autoimmunity. Sometimes an antigen is sequestered away from the reach of T cells. When such a sequestered antigen is released accidentally, the reactive T cell clones mount an attack on the tissue. A classic example is sympathetic ophthalmia. In this condition a penetrating injury to one eye exposes the uveal tissue of that eye to T cells. These T cells mount a response against the uveal tissue, recognising the hitherto hidden antigen as foreign. The results is a granulomatous uveitis in the healthy eye due to an immune-mediated injury. Yet another theory suggests that shared epitopes between a microorganism and host tissue result in an autoimmune response when the host is exposed to the microbe (also called molecular mimicry). A classic example is acute rheumatic fever; cross-reactivity between the streptococcus and the cardiac tissue results in an abnormal immune response. Alternatively the basis of autoimmunity may lie in the presence of abnormal autoreactive clones due to mutations or due to defects in the function of T cells. Irrespective of the particulars of the models studied, there seems to be a strong genetic predisposition to the condition.

17.2 Approach to a patient with arthritis

Acute Arthritis

Arthritis is defined as objective clinical evidence of the inflammation of a joint. Pain and swelling of the joint are evidence of arthritis. When there is pain in a joint but no evidence of swelling is present, the term *arthralgia* is used. When the inflammation is restricted to a single joint, the term *monoarthritis* is used. When 2–4 joints are involved, the condition is termed *oligoarticular arthritis*. When more than four joints are inflamed, the term *polyarthritis* is used. Arthritis of less than six weeks duration is considered *acute*.

Clinical approach When evaluating a patient with acute arthritis, the number and type (small versus large joints, lower limb versus upper extremity) of joints affected, pattern (symmetrical versus asymmetrical) and temporal profile of joint inflammation, the course and the presence of extraarticular symptoms aid in diagnosis.

Acute monoarthritis is most often infectious in origin. A majority of cases are bacterial (with *Staphylococcus aureus* as the predominant pathogen); tuberculosis, fungi, and viral agents cause monoarthritis less frequently. Acute gout should also be considered in the differential diagnosis. Less common causes of monoarthritis include trauma (with hemarthroses), a foreign body, ischemic necrosis, and systemic diseases (Reiter and Behcet syndrome).

The causes of acute polyarthritis are enumerated in Table 17.2. The temporal profile of joint involvement may be simultaneous, additive or migratory. The *simultaneous pattern* is characterised by the involvement of several joints all at the same time; examples include infective arthritis, gout and systemic immuno-inflammatory diseases. In the *additive pattern*, new joints are involved successively without the resolution of previously-affected joints; examples include infective arthritis, reactive arthritis, Still's disease, seronegative spondylo-arthropathies and other systemic diseases. In the *migratory pattern*, inflammation in previously affected joints subsides as new joints become involved; examples include rheumatic fever, gonococcal arthritis, and Lyme disease. It is possible that different patterns of arthritis occur during the course of a disease.

Bacterial arthritis has a simultaneous or additive onset, and fever is a prominent feature. Radiographs are of limited diagnostic utility as

Table 17.2 Causes of acute polyarthritis

1. Symmetrical
   - rheumatic fever
   - gonococcal infection
   - serum sickness
   - erythema nodosum
   - vasculitis syndromes
   - viral infection
   - connective tissue disease
   - gout
2. Asymmetrical
   - reactive arthritis
     - urethritic type
     - enterocolitic type

the typical subchondral rarefaction and subchondral bone erosion emerges over 12–20 days. Arthrocentesis with Gram staining and culture of the joint fluid is often diagnostic. Polyarthritis is also common in some viral illnesses; the prodromal phase of hepatitis B infection, the clinical phase of rubella and parvo virus B19 infection can manifest with arthritis as a prominent feature.

Behcet's disease is an illness of autoimmune origin characterised by recurrent painful aphthous oral and genital ulcers along with eye involvement (uveitis, occasionally recurrent hypopyons) and skin disease (folliculitis, and increased dermal reactivity[1]). Arthritis can be a component of Behcet's disease with the knees and ankles affected most often. Still's disease is a rare but important cause of polyarthritis especially when there is associated high grade fever. Young adults are most often affected and there may be an evanescent pruritic rash. When in addition to polyarthritis there are skin lesions, a mononeuritis multiplex or microscopic hematuria is present, a systemic vasculitis should be suspected as the etiologic cause of polyarthritis.

Migratory arthritis is classically seen in rheumatic fever and gonococcal arthritis. Inflammation in the joints initially involved subsides as new joints become involved, and typically both diseases affect large peripheral joints (ankle, knee, elbow, wrist). The evolution of arthritis in the two diseases is, however, different. Gonococcal arthritis progresses more showly and eventually tends to localise to a single joint. The involvement of tendon sheaths with tenosynovitis of hands, feet and Achilles' tendon is highly suggestive whereas ankle joint involvement is less common (compared to rheumatic fever). The presence of painful hemorrhagic or pustular skin lesions 'around' the joints is also highly characteristic of gonococcal arthritis. Rheumatic fever occurs in the 5–15 years age group whereas gonococcal arthritis occurs in the older, sexually active age group. The additional presence of a cardiac murmur or a pericardial friction rub strengthens the diagnostic possibility of rheumatic fever.

Reactive arthritis is seen more often in adults with a history of a mild urethritic or enterocolitic illness about two weeks earlier. The arthritis is asymmetrical, involves the lower limbs more often and tenosynovitis or *enthesitis* (insertion tendonitis manifesting as heel pain) may be prominent.

In erythema nodosum, the typical subcutaneous nodules on the anterior aspect of the leg are prominent and there is a marked predilection for the ankle joint. Systemic lupus erythematosus can, on occasion, present as polyarthritis but other clinical features (see later section) suggesting a multisystem disease are usually evident. Gout can also rarely present in a polyarticular form and the involvement of toes, insteps of heels and ankles is then typical.

The laboratory investigations obtained depend on the diagnostic possibilities. If rheumatic polyarthritis is likely, serum antistreptolysin O titres can be obtained as well as the throat swab processed in an attempt to culture the β hemolytic streptococccus. In suspected gonococcal arthritis, the joint fluid is aspirated and cultured. The diagnostic yield is, however, only 50 per cent but the isolation of purulent fluid itself warrants a trial of parenteral penicillin. If gout is likely, the joint fluid is examined with a polarised light microscope for the presence of the typical needle-shaped crystals, and serum uric acid levels are obtained concomitantly.

Chronic polyarthritis

When inflammation of several joints has been present for more than six weeks, chronic polyarthritis is diagnosed. The causes of chronic polyarthritis are enumerated in Table 17.3.

Where the disorder progresses very slowly without 'flares' and in the absence of morning stiffness, degenerative joint disease is a likely

[1] The term *pathergy* is used to describe this heightened reactivity to scratches or injection of saline: sterile pustules develop.

possibility. The disorder typically affects perimenopausal women and the usual finding is coarse crepitus of the affected joint. Weight bearing joints are more affected and the shoulders, elbows and wrists are spared. In the hands, the distal interphalangeal joints (with bony spurs called *Heberden nodes*) and the proximal interphalangeal joints (with *Bouchard nodes*) are typically involved but the metacarpophalangeal joint is spared. Pain and stiffness worsen with activity and the 'end-of-the-day' hours can be particularly difficult.

In metabolic arthropathies or deposition arthropathies, the clinical pattern is variable but the 'feel' of the joint may be suggestive. In chronic tophaceous gout, the joint feels irregular and lumpy, and in amyloidosis the joint appears 'puffy' (*shoulder pad sign*).

Rheumatoid arthritis is typically seen in young women and periodic exacerbations are characteristic. Maximum disability is felt in the morning (after a night's rest) and is experienced as 'morning stiffness' which lasts for half an hour or more. The joints show objective evidence of inflammation in the form of effusions. There is a predilection for involvement of the metacarpophalangeal, metatarsophalangeal and the proximal interphalangeal (PIP) joints. The distal interphalangeal (DIP) joints are spared. Tendon sheath effusions may be seen. Subcutaneous nodules, when present, are highly suggestive of the disorder.

Seronegative spondyloarthropathy (SSA) is a heterogeneous group of disorders which must be considered a diagnostic possibility if the affected person is a young male, has joint involvement which is asymmetrical and predominantly below the hip, has prominent spine involvement or symptoms of enthesopathy (such as heel pain).

If fever, weight loss and other multisystemic symptoms are prominent in a patient with chronic polyarthritis, the possibility of connective tissue disease or systemic vasculitis must be considered.

The presence of digital clubbing and prominent bowel disturbances arouse suspicion of arthritis associated with inflammatory bowel disease. Destruction of cartilaginous structures made of 'elastic cartilage' (floppy ear and saddle nose) suggest the rare disorder of *relapsing polychondritis.*

In the laboratory investigations, the most useful tests include X-rays of the affected joint, test for rheumatoid factor in serum, and measurement of serum uric acid. The presence of HLA B-27 favours a diagnosis of seronegative spondyloarthropathy.

Table 17.3 Causes of chronic polyarthritis

1. Symmetrical
   - rheumatoid arthritis
   - degenerative joint disease
   - crystal-induced arthritis
   - other metabolic arthritis (amyloidosis)
   - connective tissue diseases
   - vasculitic syndromes
   - relapsing polychondritis
   - Whipple's disease
   - juvenile rheumatoid arthritis
   - Behcet syndrome
2. Asymmetrical
   - seronegative spondyloarthropathies

KEY CONCEPTS

Arthritis

➢ Important clues to the etiology of an arthritic syndrome can be obtained by ascertaining if the arthritis is acute or chronic, determining its distribution (symmetrical versus asymmetrical; axial versus peripheral; mono-, versus pauci- versus polyarticular involvement) and by enquiring into the presence or absence of associated systemic features.

➢ Important causes of an acute monoarthritis include crystal-induced synovitis (gout), infection (septic arthritis), trauma (hemarthroses, serous effusion) and tumour. The occurrence in a middle-aged male, involvement of the first MTP joint, the presence of exquisite pain and documentation of hyperuricemia substantiate a diagnosis of gout. A history of a septic focus, surgery or aspiration of a joint, the presence of prosthesis, a history of drug abuse and high fever help identify septic arthritis. A diagnostic arthrocentesis with synovial fluid analysis is the investigation of choice.

➢ Acute polyarthritis may be due to viral arthritis (rubella, hepatitis B), gonococcal arthritis, acute rheumatic fever, reactive arthritis or Lyme disease. Viral arthritis is identified by the presence of other systemic symptoms and signs (rash and occipital adenopathy in rubella; jaundice in hepatitis B). Onset in a sexually active woman after the menstrual periods, the presence of tenosynovitis, hemorrhagic skin lesions (especially with a perifollicular distribution) suggest a diagnosis of gonococcemia with arthritis. In acute rheumatic fever, the arthritis typically affects a child (5-15 years), follows a migratory pattern, affects both the large and small joints and there may be evidence of carditis (murmur/pericardial friction rub) and a history of preceding sore throat. When polyarthritis occurs in a young man, involves the lower extremity, is associated with mucocutaneous or conjunctival lesions, reactive arthritis is the likely diagnosis. A history of preceding urethritis or enterocolitis is corroborative. Blood cultures, ASLO titres, and synovial fluid analysis help establish a diagnosis.

➢ Chronic polyarthritis may be due to rheumatoid arthritis, osteoarthritis, seronegative spondylo-arthropathy (SSA), psoriasis, a metabolic cause (amyloidosis) or sarcoidosis. A history of morning stiffness, relief with activity, sparing of the DIP and involvement of the MCP joint, soft tissue swelling suggest a diagnosis of rheumatoid arthritis. Serologic evidence of rheumatoid factors and radiologic evidence of bony erosions is confirmatory. Occurrence in an elderly subject, typical involvement of the DIP, a history of joint stiffness which improves with rest, the presence of bony swelling without tenderness suggests osteoarthritis. A normal ESR and radiologic evidence of osteophytes further substantiates the diagnosis. A history of preceding psoriasis of the skin, involvement of the DIP and pitting of the nails suggests psoriatic arthropathy. Involvement of the spine and sacroiliac joints, an asymmetrical below-hip polyarthritis, prominent heel pain suggests a diagnosis of seronegative spondyloarthropathy.

7.3 Diagnostic methods in clinical immunology

Clinical examination of joints

Inspection, palpation and determiation of the *range of motion of joints* permits an assessment of joint function and dysfunction. Joint pain on moving a joint usually suggests joint disease. Joint motion is often painless in disease of bone, soft tissues or periarticular tissues. A swollen joint that is red and has increased heat over its surface is obviously inflamed. All swollen joints must be *ballotted* to elicit the presence of fluid. Absence of 'ballottement' in a swollen joint may indicate synovial thickening, or capsular or bony enlargement rather than a simple effusion. *Crepitus* refers to the 'crackling' feel one gets while moving a joint. Crepitus may arise from tendons or from intraarticular structures. Detection of small effusions of the knee joint is facilitated by the *bulge sign*. With the patient supine and knee extended, the medial aspect of the knee joint is stroked so that the normal hollow is visible and any fluid is expressed away. Then with one hand on the suprapatellar pouch the other hand presses gently on the lateral aspect of the knee. If fluid is present in the knee joint, a fluid wave or bulge is visible on the medial aspect.

Laboratory investigations in immune disease

Acute phase reactants Acute phase reactants are non-specific indicators of inflammation of any etiology and include the erythrocyte sedimentation rate, C-reactive protein, serum amyloid A protein, fibrinogen, and haptoglobin. Of these, the most frequently measured ones are the ESR and C-reactive protein.

The ESR appears to be of help in diagnosis especially when it is elevated to more than 100 mm / first hour. Such high values are seen in very few conditions, notably multiple myeloma, giant cell arteritis, polymyalgia rheumatica and chronic infections. The C-reactive protein is an acute phase reactant which is produced by the hepatocytes and that rises and falls rapidly. It is also a non-specific indicator of inflammation but is more useful than ESR in some instances. Thus, fever in a patient with SLE could indicate either disease activity or active infection. An elevated CRP level in this case points to a high likelihood of infection.

Rheumatoid factors Rheumatoid factors are antibodies to the F_c portion of IgG molecules. They are easily detected by the latex agglutination test. In this test, latex beads coated with IgG are allowed to react with serum from patients. If the rheumatoid factor is present in the test serum, the beads agglutinate (due to cross-linking) and the test result is positive. The rheumatoid factor is positive in upto 80–90 per cent of patients. These seropositive patients generally have more severe disease than patients without rheumatoid factors (seronegative). Rheumatoid factors are not specific for rheumatoid arthritis. They may be present in the sera of patients with other rheumatic illnesses, subacute bacterial endocarditis and other chronic inflammatory diseases.

Antinuclear antibodies (Fig 17.6) Assays for heterogeneous antibodies to nuclear constituents are widely used in rheumatic disease. These antibodies are detected by indirect immunofluorescence techniques that involve rat kidney or liver tissue. When the test serum is applied to rat tissue that has been frozen and cut to expose nuclear components, the antinuclear antibodies interact with the rat's nuclear material. This interaction can be detected by fluorescence microscopy.

A positive ANA test must be interpreted with caution because 1) the serum of a patient with any rheumatic disease may contain many auto-antibodies to different nuclear constituents, so that a 'homogeneous' pattern may obscure a 'speckled' or 'nucleolar' pattern; 2) different antibodies in the serum can be present in different titres, so that by diluting the serum one can change the pattern observed; 3) the stability of the different antigens is different and can be changed by fixation or denaturation; and 4) the pattern observed appears to be influenced by the types of tissues or cells used as substrate fo the test.

Other autoantibodies

Anti-double-stranded DNA antibodies ar specific for systemic lupus erythematosus (SLE The anti-Sm antibody is also relatively specif for SLE but is found in only a third of patient Anti-histone antibodies are seen in dru induced SLE. Anti-Ro/SSA and anti La/SS antibodies are encountered in Sjogren's diseas Antibodies to extractable nuclear antigens a seen in the mixed connective tissue diseas Anti-Jo1 antibodies are seen in dermat polymyositis. Anti-Scl-70 (anti-topoisomeras and anticentromere antibodies are seen progressive systemic sclerosis. Antineutroph cytoplasmic antibodies (ANCA) are path gnomonic of Wegener's granulomatosis.

Tests of immune function

Screening tests: Most defects of immune functio can be ruled out in a cost-effective manner

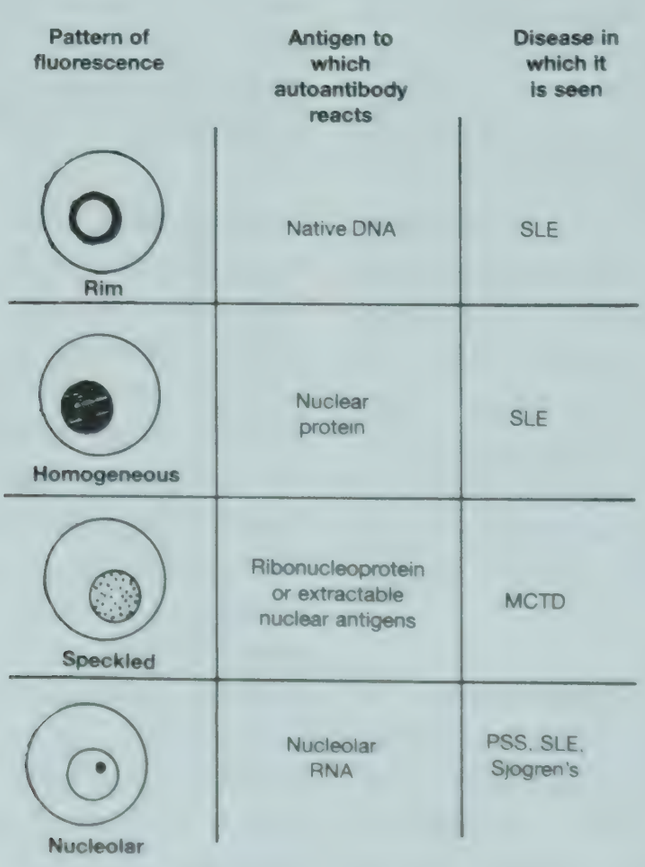


Fig 17.6 Antinuclear antibodies

nple screening tests. Of primary importance e complete and differential leukocyte counts d platelet counts. If the absolute neutrophil unt is normal, congenital neutropenia or vere chemotactic defects are unlikely. milarly, normal absolute lymphocyte count les out severe T cell defects. A normal platelet unt rules out the Wiskott Aldrich syndrome ee later section).

sts of B cell function: Measurement of turally occurring antibodies to blood group bstances A and B (called iso-hemagglutinins) useful. A titre of more than 1:8 indicates rmal IgM levels and effectively rules out most the treatable B cell defects (other than IgA ficiency). Quantification of serum IgA levels another cost-effective means of ruling out ost types of agammaglobulinemia.

sts of T cell function: Assessing T cell function particularly easy. An intradermal skin test is one with an appropriate recall antigen (purified rotein derivative [PPD] or Candida antigen). n area of skin induration of 10mm or more at 8 hours is termed a positive test. A positive test les out virtually all primary T cell defects.

omplement: Total hemolytic complement is easured in 'CH_{50} units' which is the dilution of rum required to lyse 50 per cent of indicator rythrocytes. It reflects the activity of all mplement components and is a good screening st for complement deficiencies.

hagocytic defect: The nitroblue tetrazolium dye eduction test (NBT) measures the ability of eutrophils to ingest and reduce the yellow itroblue tetrazolium dye on latex particles to a eep blue dye formazan. The reduction reaction quantitatively measured by spectrophoto-metry.

ynovial fluid analysis

ynovial fluid aspiration is mandatory in any atient with monoarthritis and an associated oint effusion. Following skin preparation with odine and alcohol and infiltration of skin with a local anesthetic agent, the joint space is entered with an 18 G needle and about 5 ml of fluid aspirated. The joint fluid is sent for analysis immediately.

Though synovial fluid analysis is seldom useful diagnostically, it is essential for the diagnosis of two treatable disorders–crystal induced synovitis (gout) and septic arthritis.

The common characteristics of joint fluid in various arthritides is shown in Table 17.4. The mucin clot test and the viscosity of joint fluid are tests that reflect the intactness of the polymeric hyaluronic acid which gives the normal joint fluid its syrupy consistency. In inflammatory arthritides the enzymes produced by inflammatory cells digest the hyaluronic acid thereby lowering the joint fluid viscosity and resulting in a poor mucin clot. Joint fluid viscosity is assessed by letting the synovial fluid fall on a surface. Normally, the fluid should string for about 1–2 inches; with low viscosity, the fluid drips like water (*string test*). The mucin clot test requires chemical reagents and is rarely done nowadays.

The joint fluid should be seen under polarised and light microscope if crystal-induced synovitis is suspected. A Gram stain should be obtained if infectious arthritis is suspected. Bloody joint fluid is encountered in hemarthrosis (following trauma or a coagulation disturbance) and in the rare disorder of pigmented villonodular synovitis.[1]

Radiology of Bones and Joints

Osteoarthritis is characterised radiologically by reduction in joint space, new bone formation in the vicinity of the articular surface (sclerosis) and the formation of marginal osteophytes. Erosions and periarticular osteopenia are not seen. The joints involved are the proximal and distal interphalangeal joints and the carpo-metacarpal joint of the thumb. Rheumatoid

[1] A disorder primarily affecting the knee joint and characterised by recurrent bloody effusions and synovial hypertrophy.

Table 17.4 Synovial fluid analysis

Characteristic	*Normal*	*Group 1 (Non-inflammatory)*	*Group 2 (Inflammatory)*	*Group 3 (Infectious)*
Prototype		Degenerative joint disease	Rheumatoid arthritis, gout	Gonococcal arthritis
Gross examination				
1. Colour	clear pale yellow	clear yellow	yellow to white	purulent
2. Clarity	clear	transparent	translucent	opaque
3. Mucin clot	good	good	fair	poor
4. Viscosity	high	high	medium	low
Microscopic examination				
1. WBCs (/mm^3)	0–200	<2000	500–20,000	>20,000
2. Polymorphonuclear cells	<10%	<30%	<30–90%	>50%
Biochemistry				
Glucose as a per cent of blood glucose	100%	100%	60–100%	<50%

arthritis is characterised by periarticular osteopenia (bone around the joint), poorly defined marginal erosions, loss of joint space and soft tissue swelling. Gouty arthritis is characterised by well-defined erosions, a relative preservation of joint space till late in the disease and an absence of periarticular osteopenia. Tophaceous deposits appear typically as soft tissue swellings with patchy calcification and with underlying punched out erosions with an overhanging edge of new bone formation. Pseudogout is evidenced by linear calcification of cartilage in areas such as the knee menisci and intervertebral discs. Ankylosing spondylitis is characterised by prominent early bilateral sacroiliitis (seen a blurred irregular joints with sclerosis), 'vertebr squaring' and fusion (*bamboo spine* Psoriatic arthritis is characterised by proxim phalangeal bone resorption, joint spac widening (*pencil-in-cup* deformity) an marginal erosions. In progressive system sclerosis there may be resorption of bone in th phalanges (*tuft resorption*) and soft tissu calcification.

Other tests

Other tests useful in select patients includ arthroscopy (looking into the joint), synovi biopsy (for synovial tumours) and bone scans.

KEY CONCEPTS

- An elevated ESR or CRP suggests inflammatory disease. The elevation of ESR serves as a reasonable marker of disease activity in both SLE and rheumatoid arthritis. CRP is not normally elevated in patients with SLE unless there is active infection.
- Latex fixation tests help to detect antiimmunoglobulin antibodies (rheumatoid factors) in patients with rheumatoid arthritis. These tests may be positive also in patients with hepatic cirrhosis, subacute bacterial endocarditis, tuberculosis and sarcoidosis.
- Antinuclear antibodies, may be positive in SLE, rheumatoid arthritis, Sjogren syndrome, PSS, and mixed connective tissue disease. The pattern of fluorescence depends on the type of antibody. Antibodies to ds-DNA result in a rim pattern, antibodies to histones cause a homogeneous (diffuse)

pattern while anti-Sm or antiribonucleoprotein antibodies result in a speckled appearance.

➢ Synovial fluid analysis may be occasionally helpful. The normal fluid is colourless, has fewer than 200 WBC/uL (<10% PMN), a high viscosity and a normal glucose content. Non-inflammatory arthritis (e.g., osteoarthritis, metabolic) is associated with a colourless synovial fluid with 200-2000 WBC/uL (<30% PMN), a high viscosity and normal glucose content. In the case of inflammatory arthritis (e.g., rheumatoid arthritis, SSA, gout), the synovial fluid has 500-20,000 WBC/uL (30-90% PMN), a decreased viscosity and a slightly low glucose content. In septic arthritis the synovial fluid is opaque, has >20,000 WBC/uL (predominantly PMN) and a marked reduction in glucose content. Needle-shaped crystals which are negatively birefringent are pathognomonic of gout (uric acid crystals), while positive birefringence suggests pseudogout (calcium pyrophosphate dihydrate).

➢ The radiologic appearance may also be helpful. Thus osteophytes are typical of osteoarthritis, syndesmophytes are characteristic of ankylosing spondylitis, a pencil-in-cup deformity is encountered in psoriatic arthritis, linear calcification of the articular cartilage is a feature of pseudogout and erosions (with reduced joint space) are suggestive of rheumatoid arthritis.

17.4 Primary immunodeficiency disorders

Primary immunodeficiency disorders are a heterogeneous group of disorders involving defects in one or more of the various components of the immune system, that is, lymphocytes, phagocytes and complement proteins. The term 'primary' is used to distinguish these diseases from 'secondary' disorders such as the acquired immunodeficiency syndrome (AIDS). A classification is provided in Table 17.5 and the associated features of common disorders are shown in Table 17.6.

Antibody Deficiency Syndromes

These disorders are characterised by the defective production of antibodies. Most patients present with recurrent sinopulmonar infections due to high grade extracellula encapsulated bacteria such as *pneumococc streptococci* and *hemophilus*. In hereditar disorders, the onset of repeated infection usually commences at the end of the first year o life when maternal antibody levels begin t wane. The body's defence mechanisms agains viruses and fungi are intact. Some disorders hav an increased incidence of autoimmune disorders Diarrhea due to intestinal infestation wit *Giardia* is also seen. Subjects with isolate deficiency of IgA have anti-IgA antibodies an can, therefore, develop anaphylactic reaction on exposure to blood products.

Table 17.5 Classification of primary immunodeficiency diseases

A. Predominantly antibody defects
1. X-lined agammaglobulinemia
2. Autosomal recessive agammaglobulinemia
3. Immunoglobulin deficiency with raised IgM
4. Isolated IgA deficiency
5. Kappa chain defect
6. Immunodeficiency with thymoma
7. Common variable immunodeficiency

B. Predominantly defects of cell mediated immunity
1. Purine nucleoside phosphorylase deficiency
2. Severe combined immunodeficiency (SCID)
3. Adenosine deaminase deficiency
4. Immunodeficiency with unusual response to EB virus

C. Immunodeficiencies with other defects
1. Transcobalamin II deficiency
2. Wiskott-Aldrich syndrome
3. Ataxia telangiectasia
4. DiGeorge syndrome

Table 17.6 Common primary immunodeficiencies

Defect	*Inheritance*	*Main associated features (besides infection)*
A. Predominant T cell defects		
1. DiGeorge syndrome	non–familial	hypoparathyroidism, cardiovascular defects, abnormal facies
2. Purine nucleoside phosphorylase deficiency	AR	hypoplastic anemia
B. Predominant B cell defects		
1. X-linked agammaglobulinemia	X-linked recessive	autoimmune disease, diarrhea, lymphoreticular malignancies
2. Selective IgA deficiency	unknown	autoimmune disorders, transfusion reaction, chronic diarrhea
3. Common variable immunodeficiency	unknown	autoimmune disease, lymphoid hyperplasia
C. Combined T and B cell defects		
1. Severe combined immuno-deficiency	AR	wasting
2. Wiskott-Aldrich syndrome	X-linked recessive	thrombocytopenia, eczema
3. Ataxia telangiectasia	AR	oculocutaneous telangiectasia, cerebellar ataxia ovarian dysgenesis, chromosomal abnormalities
D. Phagocytic deficiencies		
Chediak-Higashi syndrome	AR	albinism, giant granules in phagocytes
E. Complement defects		
1. C1, C2, C4 deficiencies	AR	autoimmune disorder
2. C6, C7, C8 deficiencies	AR	disseminated Neisseria infection
3. C1 esterase inhibitor deficiency	AD	hereditary angioneurotic edema
4. Absence of regulatory protein (decay accelerating factor)		paroxysmal nocturnal hemoglobinuria

Cellular Immunodeficiency Syndromes

tients with defects in cellular immunity pically present with recurrent infections due opportunistic organisms and low grade thogens. Affected individuals develop fection with *Candida albicans,* viruses or *eumocystis carinii.* They have a short lifespan, ve a wasted appearance and are retarded in owth. There is a higher incidence of mphoreticular malignancies as well.

Phagocytic Defects

eutrophil disorders cause patients to be lnerable to a variety of pyogenic organisms, tably *Staphylococcus aureus, Pneumococcus, coli* and *Pseudomonas aeruginosa.*

Complement System Defects

Deficiencies of early components (activation proteins of the classical pathway) are most often associated with autoimmune phenomena, usually a lupus-like syndrome.

Deficiencies of 'membrane attack complex' predispose to disseminated infection with the *Neisseria* species.

Treatment of immunodeficiency disorders

Hypogammaglobulinemic disorders are treated with monthly injections of immunoglobulins (i.m or i.v). Stem cell deficiency in SCID is treated with bone marrow transplantation, and thymic aplasia is treated with transplantation of human fetal thymus fragments.

17.5 Connective tissue disorders

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus is an immuno-inflammatory disease characterised by production of autoantibodies against nuclear, cytoplasmic and cell membrane antigens and manifested by inflammation in several body organ systems.

Epidemiology Systemic lupus erythematosus is a disease of young women. The disorder afflicts about 0.1 per cent of the general population and is more common as well as more severe in the non-caucasian races.

Etiopathogenesis The exact etiology of SLE is as yet unknown. It is characterised by an abnormal immune stimulation with loss of self-tolerance leading to an expansion of B cell clones which produce a variety of antibodies. These antibodies may form immune complexes and, thereby, cause inflammation on deposition within specific tissues or may do so directly. The clinical manifestations are caused by these auto-antibodies. The more severe the immuno-inflammation, the greater is the clinical severity of the disease. Patients with large amounts of anti-DNA antibodies, especially precipitating antibodies, are more likely to have renal disease. A defect of suppressor T lymphocytes contributes to the polyclonal B lymphocyte activation.

The triggers for this immune hyperactivity include environmental factors like drugs (hydralazine, M-dopa, phenytoin, procainamide etc), ultraviolet light (which induces ski keratinocytes to secrete B cell activators lik interleukin 1) viruses and genetic factors lik HLA (DR3) and complement deficiencie (C_2 deficiency).

Pathology Often the underlying histologica abnormality is a small vessel vasculiti characterised by a central area of eosinophili fibrinoid material, basophilic hematoxyli bodies (representing nuclear debris), granulo cytic infiltration and periarteriolar edema Splenic arteries have a typical onion peel-lik concentric fibrosis. Renal histopatholog includes several forms of glomerulonephriti which have been discussed in detail earlier.

Clinical features The American Rheumatism Association (ARA)[1] has developed criteria fo the diagnosis of SLE (Table 17.7). Though th ARA criteria are useful in the diagnostic work up for possible SLE, these are not specificall designed for establishing the diagnosis i individual cases. They are useful principally a classification criteria for grouping patients i studies or for retrospective descriptive analys of patient series.

Roughly half of SLE patients have only 'non major organ disease and the other half als develop 'major organ disease'. The clinica

[1] The ARA has now been renamed the American Colleg of Rheumatology (ACR).

Table 17.7 American College of Rheumatology Association Criteria* for systemic lupus erythematosus

Criterion	*Definition*
Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterised by tenderness, swelling or effusion
Serositis	Pleuritis – convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion (or) Pericarditis – documented by ECG or rub or evidence of pericardial effusion
Renal disorder	Persistent proteinuria greater than 0.5 g/day or greater than 3+ if quantitation is not performed (or) Cellular cast – may be red cell, hemoglobin, granular, tubular, or mixed
Neurologic disorder	Seizures – in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance (or) Psychosis – in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
Hematologic disorder	Hemolytic anemia with reticulocytosis (or) Leukopenia – less than 4000/mm^3 total on two or more occasions (or) Lymphopenia – less than 1,500/mm^3 on two or more occasions (or) Thrombocytopenia – Less than 100,000/mm^3 in the absence of offending drugs
Immunologic disorder	Positive LE cell preparation (or) Anti-DNA: antibody to native DNA in abnormal titre (or) Anti-Sm: presence of antibody to Sm nuclear antigen (or) False-positive serologic test for syphilis, known to be positive for at least six months and confirmed by *Treponema pallidum* immobilisation or fluorescent treponemal antibody absorption test
Antinuclear antibody	An abnormal titre of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with 'drug-induced lupus' syndrome.

* As revised in 1982. The criteria are not intended for diagnosis of individual cases. In clinical studies, systemic lupus erythematosus can be identified if any four or more of the 11 criteria are present, serially or simultaneously during any interval of observation.

features of SLE may therefore be divided into these two categories (Fig 17.7).

Non-major organ disease

The most common of clinical manifestations is joint pain. The arthralgia is typically transitory. With increasing severity and duration of disease a frank arthritis may develop. It is symmetric, affects the proximal interphalangeal joints of the hands, metacarpophalangeal joints, wrists and knees and is non-erosive.

The majority of patients have fever, fatigue and weight loss. The typical 'butterfly rash' is non-papular, erythematous, covering the cheeks and bridge of nose but sparing the nasolabial folds. The rash of *discoid lupus erythematosus* is characterised by a similar location but with central atrophy, follicular plugging, hyperkeratosis and telangiectasia. Roughly 50 per cent of SLE patients have diffuse alopecia or 'brittle hair'. The latter is diagnosed by the 'hair pull' test in which a lock of hair is pulled gently. In subjects with brittle hair 5–10 strands can be extracted from the scalp with the roots intact. If performed gently, the maneuvre is not painful. Painless nasopharyngeal ulcers, vasculitic skin lesions and occurrence of Raynaud's phenomenon are other mucocutaneous features of

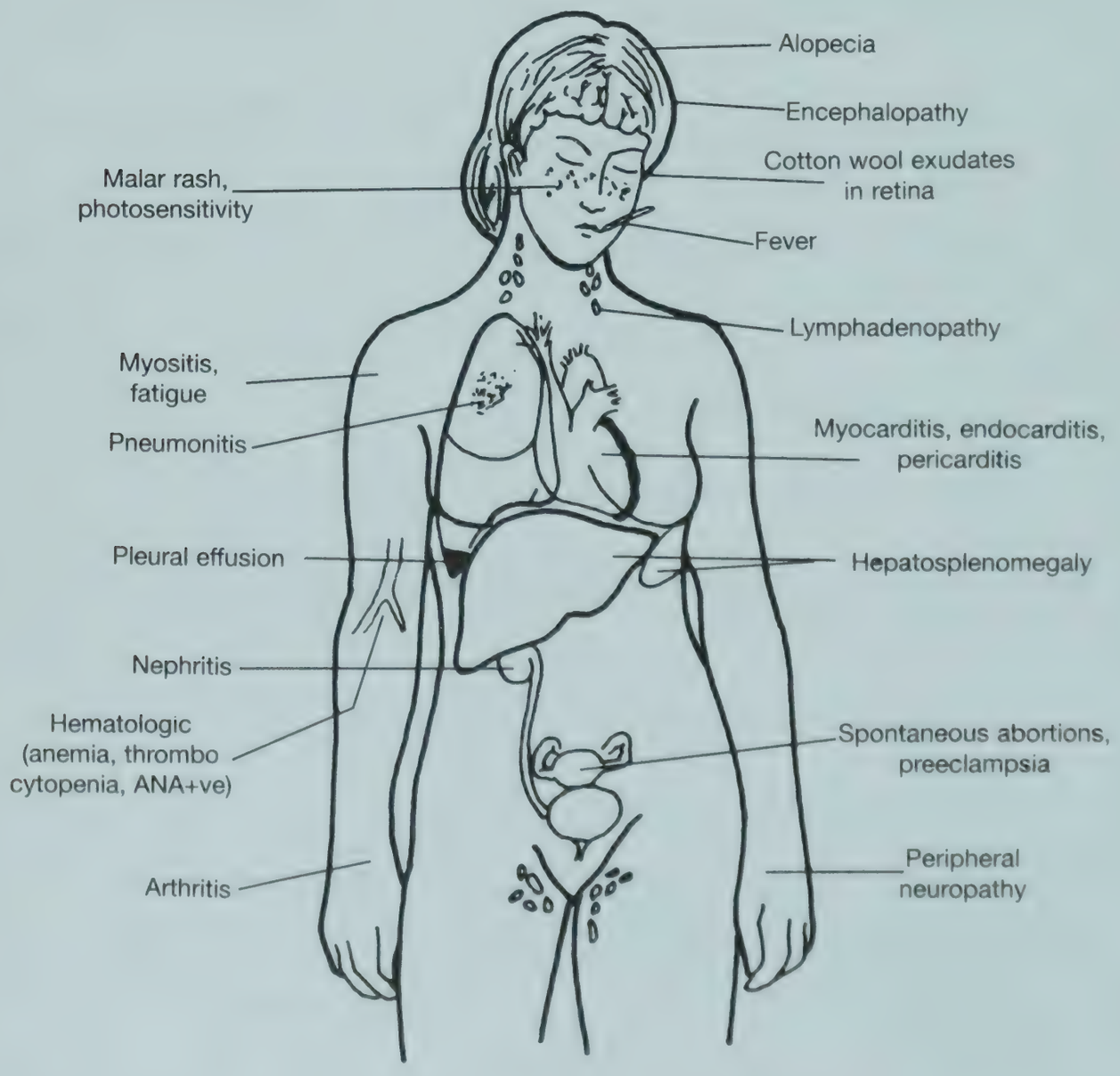


Fig 17.7 Clinical features of SLE

SLE. Myalgias occur frequently in patients though a true myositis (inflammation of muscles) is uncommon.

Polyserositis is yet another important manifestation of SLE. It refers to inflammation of the serosal surfaces of the pericardium, thorax and abdomen and manifests clinically as pain in the region of the inflamed surface. Thus, pleuritic chest pain (with or without pleural effusion), pericardial chest pain (frequently with a friction rub and electrocardiographic findings) and diffuse abdominal pain may all form part of the clinical features.

Major organ disease

Renal disease is one of the important causes of morbidity and mortality and is discussed in Chapter 14. It may present as an active urinary sediment with leukocyturia and hematuria with or without azotemia. Hypocomplementemia and high levels of anti-native deoxyribonucleic acid antibodies are associated with nephritis.

The central nervous system is also involved frequently in SLE. It may take the form of an encephalopathy, seizures, focal deficits or in rare cases choreiform movements. Retinal involvement is evident as cytoid bodies on ophthalmoscopic examination. The involvement of the peripheral nervous system is usually due to vasculitis of the vasa nervorum and usually takes the form of a mononeuritis multiplex. The musculoskeletal system may occasionally be involved with a mild myositis evident as raised serum levels of enzymes: create phosphokinase (CPK) and lactate dehydrogenase (LDH) .

The cardiovascular system may also be involved with valvulitis (and resultant valvular regurgitation) and myocarditis (evident as myocardial failure and/or arrhythmias).

The involvement of the hematological system is often an important clinical feature of SLE. Leukopenia and thrombocytopenia are frequent with disease activity[1]. Severe thrombocytopenia can result in bleeding and a presentation like idiopathic thrombocytopenic purpura (ITP). In fact, a patient presenting initially with ITP can go on to develop the full-fledged clinical picture of SLE. Two types of antibodies to the clotting factors can occur in patients with SLE. The more common antibody is the antibody to phospholipids (*antiphospholipid antibodies*) which result in a false positive VDRL test and can lead, on occasion, to venous thromboses or recurrent abortions. The other type of antibody is rare but clinically more problematic, that is, antibodies to coagulation factors which can result in severe coagulopathy.

Investigations With disease activity, the ESR is elevated, the leukocyte and platelet counts decreased and CRP levels normal. Antinuclear antibodies are present in more than 95 per cent of patients. Hypocomplementemia and anti-double-stranded DNA antibodies are very frequent. Urinalysis may reveal leukocyturia and red blood cell casts. A '*telescoped*' urine deposit (see earlier Renal section) is very characteristic.

Treatment Mild disease exacerbations are treated with adequate rest and avoidance of drugs which can further exacerbate the disease such as, penicillins, erythromycin and oral contraceptives. Avoidance of exposure of the skin to the sun is recommended for photosensitive patients. Sunscreen lotions like paraaminobenzoic acid can be used.

For non-organ manifestations, hydroxychloroquine (200 mg per day) is effective. Non-steroidal antiinflammatory drugs are useful to control arthritis, arthralgias, fever and serositis.

The involvement of organ systems is an indication for the use of glucocorticoids. For life-threatening disease, intravenous *pulse therapy* is indicated, that is, 500 mg methyl prednisolone is given by i.v. infusion over 30 minutes every day for 3–5 days. Prednisone 50 mg po b.i.d. is then begun and slowly tapered. For non-life-threatening major organ disease, oral

[1] In Asians, a *hemophagocytic syndrome* has been described with fever, fulminant pancytopenia and bone marrow evidence of phagocytosis of hemopoietic cells.

prednisolone can be started. An alternate day schedule is recommended to reduce any untoward effects of long term glucocorticoid therapy.

Immunosuppressive agents can also be used, usually in patients refractory to glucocorticoids or for their steroid sparing effects. The early use of cyclophosphamide especially as *pulse therapy* (0.5–1 g/m^2) in active lupus nephritis may improve renal function.

Plasmapheresis has also been used in SLE patients in an attempt to reduce circulating immune complexes. It is, however, expensive.

Transplantation and chronic hemodialysis have been utilised in patients with lupus nephritis and end-stage renal disease.

The use of immunosuppressive therapy has improved the prognosis of SLE patients and the 10-year survival is now more than 90 per cent.

Progressive Systemic Sclerosis

Progressive systemic sclerosis (PSS) is a multisystem disorder of unknown etiology characterised by widespread vascular sclerosis (small vessel obliterative disease) and fibrosis of skin and other visceral organs.

Epidemiology PSS is a disease of adulthood (30-50 years) with a predominant affliction of women (F:M=4:1). There is an increased incidence of disease in coal miners exposed to silica dust and in industrial workers exposed to vinyl chloride.

Etiopathogenesis The etiology of PSS is multifactorial with both genetic and environmental factors contributing.

There is an association with the major histocompatibility complex HLA B8, DR 3 haplotypes. Environmental factors include exposure to certain chemicals such as silica dust, vinyl chloride, epoxy resins, solvents and exposure to some drugs, such as, bleomycin, carbidopa, pentazocine and cocaine.

Immune abnormalities of both humoral and cellular systems have been described. Vascular and endothelial cell proliferation precede fibrosis in the affected tissue. Perhaps an abnormal immune response to certain components of the blood vessel wall (Type I and IV collagen and laminin) initiate injury. This results in the release of cytokines and excess stimulation of fibroblasts resulting in excess collagen synthesis.

One of the tissues most accessible to observation (and therefore of clinical use) is the nailfold capillary loops. In PSS there is initially capillary dilatation which is soon followed by areas of capillary dropout.

Clinical features and classification (Fig 17.8) PSS has been divided into the clinical subsets of *localised* and *generalised* disease. Localised scleroderma affects only the skin and is further divided into plaque-like lesions (*morphea*) or linear lesions (*linear* scleroderma). Generalised disease is also divided into two clinical subsets limited and diffuse systemic sclerosis.

Limited systemic sclerosis

This is a benign disorder with cutaneous involvement restricted to the extremities, late involvement of the lungs and other viscera and the serologic presence of anticentromere antibodies. The skin over the digits becomes taut and leads to the typical appearance of sclerodactyly. Calcification of the skin and telangiectasia are other cutaneous features.

The combination of calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia is referred to as the 'CREST' syndrome.

Diffuse systemic sclerosis

This is a more lethal disorder with the involvement of truncal skin, early involvement of viscera, and the serologic presence of antitopoisomerase antibodies (anticentromere antibodies are absent).

Skin involvement in PSS is universal and is initially manifested as puffy edematous skin over the hands and feet. This progresses usually over

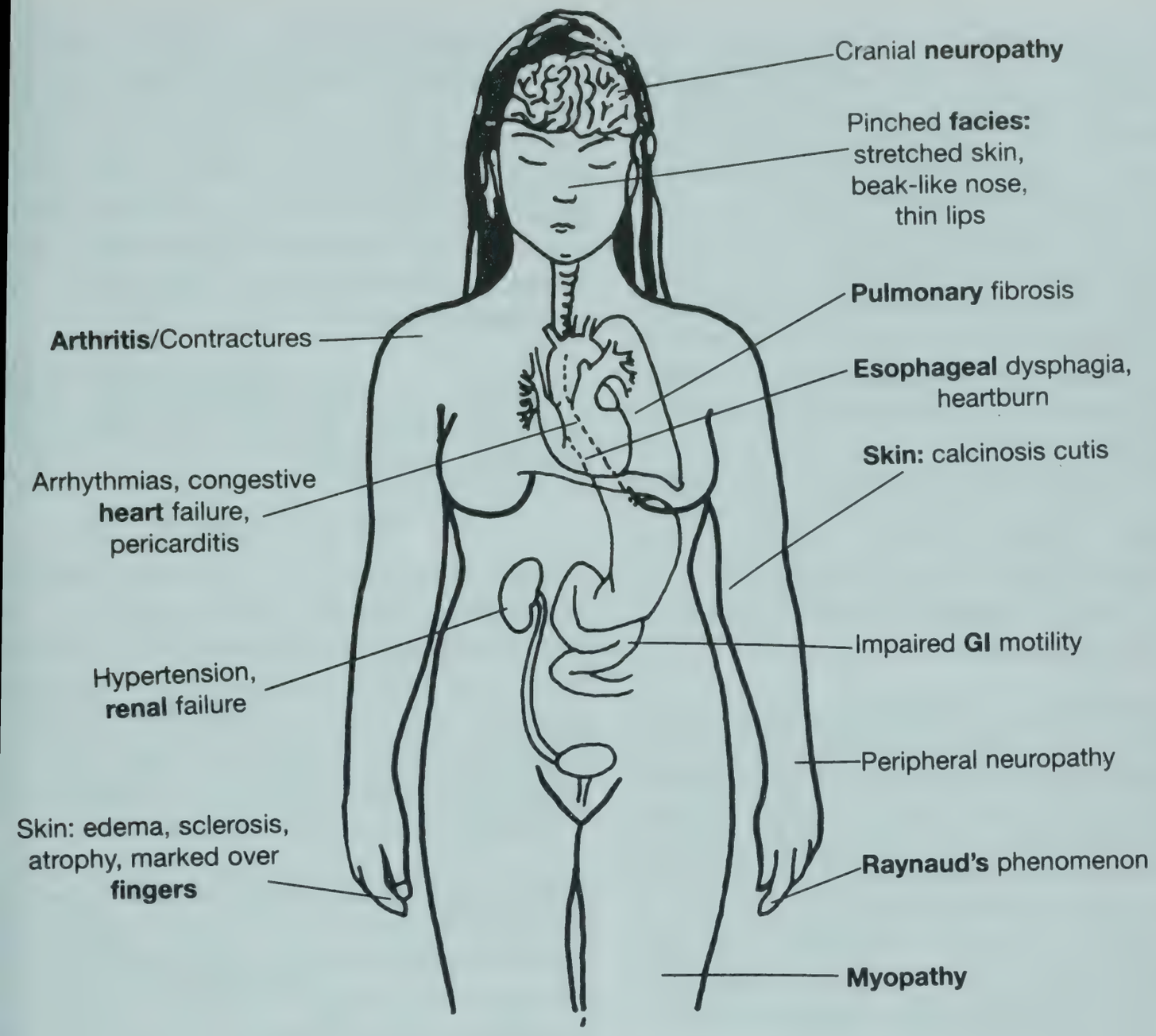


Fig 17.8 Progressive systemic sclerosis: clinical features

some years, to the indurated stage characterised by shiny, taut, hidebound skin with hair loss and diminished sweating. When the skin over the joints is affected, there is limitation of joint movement and development of contractures. Skin changes are almost always associated with Raynaud's phenomenon. Raynaud's phenomenon is the classic triphasic colour change — pallor, cyanosis, rubor (red) — in sequence with pain and tingling of the extremities. It may precede skin involvement by several years.

Involvement of esophageal musculature is seen in 90 per cent and manifests as esophageal motility dysfunction. Dyspeptic symptoms due to reflux esophagitis and dysphagia are prominent symptoms. Involvement of the small bowel is reflected by hypomotility of the small intestine with diarrhea due to stasis and bacterial overgrowth.

Pulmonary involvement is also very common and takes the form of diffuse interstitial fibrosis. Exertional dyspnea is the most common symptom and tachypnea with bibasilar rales are evident on examination. Severe pulmonary disease can lead to pulmonary hypertension and cor pulmonale. There is an increased incidence of alveolar cell carcinoma in PSS patients. Pleural involvement is unusual in PSS patients.

Renal involvement is seen in over 50 per cent of patients. It manifests as proteinuria, hypertension and azotemia. It is related to internal proliferation of interlobular arteries. Some patients develop malignant hypertension, a microangiopathic hemolytic anemia and rapidly progressive renal failure. This is related to spasm of small renal arteries with renal cortical ischemia and massive renin-angiotensin release.

Fibrosis of the myocardium can result in cardiomyopathy, and fibrosis of the conduction system manifests as arrhythmias and conduction blocks.

Joint complaints are frequent and tendon sheath involvement is common (evident as audible tendon friction rubs). Muscle involvement may also occur usually taking the form of a mild indolent myopathy with minor elevation of enzymes.

Investigations Laboratory investigations include an elevated ESR and hyperglobulinemia. Urinary sediment abnormalities usually reflect renal involvement. Pulmonary function testing reveals restrictive lung disease, and a barium cineradiograph of the esophagus demonstrates decreased or absent peristalsis of the distal esophagus. Antinuclear antibodies (speckled pattern) are detected in serum in 75 to 90 per cent of patients, and rheumatoid factor in 25 per cent. Demonstration of antibody to centromere or to topoisomerase I (Scl 70 antigen) is more specific. Nailbed capillaroscopy has already been mentioned as an important investigation.

Management There is no treatment which has been shown to alter the natural history of the disease. D penicillamine (500 to 1500 mg daily) and colchicine have been used to prevent collagen cross-linking but their long term effects are uncertain. Skin softening is seen as a short term effect. Raynaud's phenomenon is managed by the prophylactic use of mittens in cold weather and the avoidance of smoking. Calcium channel blockers are effective in some patients. Corticosteroids have been used for pulmonar fibrosis and H2 receptor blockers alongwit sucralfate have been used for reflux esophagiti Patients with intestinal malabsorption respon to broad spectrum antibiotics like tetracycline Renal involvement is managed conservatively aggressive control of hypertension wit converting enzyme (ACE) inhibitors is a important measure.

Prognosis Renal, pulmonary and cardia involvement all portend a poor outcome as doe diffuse systemic illness.

Sjogren Syndrome

Sjogren syndrome is a chronic immuno inflammatory disorder characterised by th inflammation and dysfunction of the exocrin glands, particularly the salivary and lacrima glands. It exists as a primary form or as a secondary form (associated with anothe rheumatic disease such as SLE, rheumatoi arthritis or PSS).

Pathophysiology and clinical features Sjogre syndrome is characterised by the lymphocyti infiltration of the exocrine glands resulting in th destruction of glandular tissue. Involvement o the lacrimal gland results in decreased tea production and a sensation of grittiness in th eye (*xerophthalmia*). The *Schirmer test* detect tear production: at least 5 mm of a filter paper i wetted in five minutes when placed in a unanesthetised eye. Severe dryness results i corneal involvement (detected by slit lamp) with erosions (*keratoconjunctivitis*). Salivary gland involvement results in a dry mouth (*xerostomia*). The two together are referred to as the '*sicca syndrome*'. The parotid glands may be enlarged firm and slightly tender. Involvement o eustachian tube mucosa results in inspissation o secretions and otitis media. Dyspareunia may occur due to dryness of the vagina. Arthritis is evident in a third of patients.

Laboratory features Auto-antibodies to the Ro (SS-A) antigen and the La (SS-B) antigen can be detected.

Management Treatment is symptomatic with frequent drinks of water and methyl cellulose eye drops to keep the conjunctiva wet. Patients with primary Sjogren syndrome are at increased risk of developing a non-Hodgkin's lymphoma.

Mixed connective tissue disease

This group of diseases is characterised by clinical features common to systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis and polymyositis; hence, it is also called the *overlap syndrome*. The typical patient is a middle-aged woman who has polyarthritis, esophageal dysfunction, fever, muscle pain and a high titre of antibodies to ribonucleoproteins (also called the *extractable nuclear antigens*). The prognosis is generally like that of systemic lupus erythematosus and the treatment follows similar lines. Minor illness without organ involvment is managed with antiinflammatory drugs, and hydroxychloroquine. Organ involvement and life-threatening disease may necessitate the use of steroids.

KEY CONCEPTS

Systemic lupus erythematosus

- SLE is a chronic immunoinflammatory disease of autoimmune origin which typically presents with multisystem involvement. Non-organ-specific antinuclear antibodies are the hallmark of SLE.
- Females are more often affected (9:1). There is an association with HLA DR2 and DR3 and with deficiency of complement components C_2 and C_4. Drug-induced SLE is a variant (INH, d-penicillamine, procainamide, hydralazine).
- Clinical features include fever, arthralgia, photosensitivity (malar rash), painless oropharyngeal ulcers, recurrent abortions, pleuropericarditis, myocarditis, renal involvement (glomerulonephritis), hemolytic anemia (with or without thrombocytopenia), retinal cytoid bodies and varied neurologic complaints (seizures, hemiparesis, peripheral neuritis).
- Laboratory investigations reveal leucopenia, elevated ESR, normal CRP (unless there is infection), false positive tests for syphilis, and positive antinuclear antibodies (anti-ds DNA and anti-Sm are specific for SLE). Urinalysis and 24-hour urinary protein estimation are important to assess lupus nephritis.
- Patients with mild disease require NSAIDS (for joint pains), sunscreen creams (for photosensitivity) and advice to avoid antibiotics which can exacerbate the condition (penicillin group is typical). Hydroxychloroquine may be effective if joint pains are disabling. Steroids are indicated for systemic disease (renal/cardiac/neurologic/hematologic involvement). Pulse doses of methylprednisolone (1g/d x 3) are used for acute exacerbations. Immunosuppressive drugs and plasmapheresis have a role in florid cases with steroid-resistance. The overall 10-year survival exceeds 90 per cent. Adverse prognosis factors include young age, CNS/renal involvement.

Progressive systemic sclerosis

- PSS is a chronic disorder characterised by thickening of the skin and tissue fibrosis. Pathologically, there is obliterative endarteritis and collagen accumulation.
- Females are more often affected and there is an association with silicosis. PSS may be diffuse (generalised) or limited (CREST syndrome).
- Clinical presentation is with Raynaud's phenomenon, sclerodactyly, taut shiny skin (puckered face, pinched nose), arthralgia, reflux esophagitis, dysphagia, lung fibrosis (with risk of cor pulmonale, and rarely, alveolar cell Ca), renal involvement with hypertension (accelerated hypertension and microangiopathic hemolytic anemia) and cardiac involvement (arrhythmias are typical).
- Laboratory investigations include nail bed capillaroscopy (abnormality of capillary loops), chest X-ray (for assessment of pulmonary fibrosis), and evaluation for antinuclear antibodies (nucleolar fluorescence), anticentromere antibodies (limited disease) and the Scl-70 antibody (diffuse disease).

- ➢ Management includes protection of the skin (d-penicillamine may have a role), keeping extremities warm (calcium channel blockers may have a role), control of hypertension (ACE inhibitors have a role), use of corticosteroids (for pulmonary fibrosis) and H2 blockers (for reflux esophagitis).

Sjogren syndrome

- ➢ This is a chronic autoimmune disease characterised by the lymphocytic infiltration of lacrimal and salivary glands. It may be primary (HLA DR3) or secondary (HLA DR4; rheumatoid arthritis, PSS, SLE).
- ➢ Females are more often affected. The presentation is with dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). The lacrimal and parotid glands may be enlarged and palpable and there is a propensity for parotitis. Patients with enlarged glands are at risk of developing a lymphoma.
- ➢ Investigations may reveal positive ANA or rheumatoid factor, and positive anti-Ro and anti-La antibodies. The Schirmer test is used to evaluate adequacy of tear secretions.
- ➢ Treatment includes maintaining good oral hygiene, and the use of artificial tears and sialogogues.

17.6 Vasculitis

Vasculitis is a term used for a group of clinically disparate disorders characterised by inflammation of the blood vessel wall (Table 17.8).

Pathogenesis Inflammation within the wall of the blood vessels in various 'vasculitic syndromes' results in a compromise of the vessel lumen with resulting ischemic changes in the tissues supplied by the vessels.

In these disorders circulating immune complexes appear to play a central role. These complexes deposit in the vascular walls, fix complement and thereby attract inflammatory cells. The inflammatory cells release enzymes which damage the vessel wall. On occasions, the immune complexes trigger off a granulomatous reaction in the vessel wall (granulomatous vasculitis). The manifestations of the individual disorders vary depending on the size of the vessel involved, the type of immune response mediated, the physical and biochemical properties of the immune complexes, the ability of the reticuloendothelial system to clear the immune complexes and the genetically determined variations in the host response.

The diagnostic possibility of vasculitis is to be kept in mind whenever there is a multisystem disease either synchronously or sequentially with constitutional symptoms or when a vascular event such as a cerebrovascular accident or claudication occurs in an unusual clinical setting (for instance, stroke in a young individual). Arthralgias, arthritis and myalgias are common and constitutional symptoms such as fever, weight loss and malaise occur in 90 per cent of patients. Renal involvement occurs in about half the patients. It may be the result of a renal arteritis or a glomerulitis, is evidenced by an active urinary sediment and is accompanied by systemic hypertension. Abdominal pain without localising findings may be prominent and is related to mesenteric arteritis or sterile peritonitis. Involvement of the vasa nervorum of nerves results in a peripheral neuropathy, typically in a mononeuritis multiplex pattern. Involvement of cranial vessels can result in focal deficits. Skin lesions are also highly specific for vasculitis and depend on the size of the vessel involved. Involvement of small vessels results in splinter hemorrhages, ulcers or gangrene. Involvement of medium-sized vessels manifests as *palpable purpura.* In leukocytoclastic vasculitis the physicochemical properties of the immune complexes are such that they are more prone to deposit in sites of higher hydrostatic pressure, the postcapillary venules, and, therefore, palpable purpura are prominent in the lower extremities. When the vessels in the deep dermal panniculus are inflamed (*panniculitis*) tender, indurated red nodules appear on the shins, buttocks and arms (erythema nodosum).

Churg-Strauss syndrome is a granulomatous disease affecting the pulmonary airways. Typically, a patient with longstanding asthma develops eosinophilia and evidence of vasculitis (skin rash, palpable purpura). Wegener's granulomatosis is a disease of unknown etiology

Table 17.8 Classification of vasculitis

	Systemic necrotising vasculitis	*Leucocytoclastic* angiitis*	*Giant cell arteritis*
Prototype	polyarteritis nodosa	Henoch Schonlein purpura serum sickness	temporal arteritis Takayasu's arteritis
Involved vessels	small and medium size muscular arteries	postcapillary venules	large and medium arteries
Histology	necrotising inflammation, acute and healing lesions	necrotising inflammation, lesion in same stage	inflammation without necrosis giant cells
Clinical organ involved	major arterial ischemic lesions (sparing lungs and spleen)	skin involvement dominant (palpable purpura)	large arteries and its branches
Diagnosis	angiography	skin biopsy	temporal artery biopsy/angiography
Therapy	corticosteroids and cytotoxic agents	supportive	corticosteroids

* Leucocytoclastic - refers to the 'nuclear debris' which is seen after polymorphonuclear cells disintegrate. Also called *hypersensitivity vasculitis.*

characterised by necrotising granulomatous inflammation of the upper annd lower respiratory tract, skin, and the kidneys. Pain over the paranasal sinuses, epistaxis, nasal ulcers are typical. Renal involvement predominates in the clinical picture eventually and determines the prognosis. The presence of antineutrophil cytoplasmic antibodies is pathognomonic.

The diagnostic test in suspected vasculitis is the biopsy of the affected tissue/organ. Sites with high yield include skin lesions, the sural nerve (if nerve conduction is abnormal), tender muscles (or blind muscle biopsy) or biopsy of tender epididymal nodules in suspected polyarteritis nodosa; nasopharyngeal biopsy in suspecte Wegener's granulomatosis and biopsy o the temporal artery in suspected giant ce arteritis.

The treatment of vasculitic syndromes i variable depending on the specific condition Thus, leukocytoclastic vasculitis has an excellen prognosis without specific treatment. Th steroid-responsive syndromes include giant ce arteritis and SLE-related vasculitis. Syndrome requiring alkylating agents like cyclophos phamide include Wegener's granulomatosis polyarteritis nodosa and rheumatoid arthritis related vasculitis.

KEY CONCEPTS

Vasculitis

- Vasculitis refers to necrosis and inflammation within the blood vessel wall. It is usually related to the deposition of immune complexes in the wall, fixation of complement and the attraction of inflammatory cells by the chemoattractants released in situ.
- The physicochemical characteristics of the immune complexes influence the type of vessel affected and this along with specific host responses affects the clinical manifestations. Clinical features which suggest a diagnosis of vasculitis include multisystem involvement, palpable purpura, pulse deficits or bruits, mononeuritis multiplex, vessel wall tenderness or nodules, urticaria and arthralgia.

- Hypersensitivity vasculitis (Henoch-Schonlein purpura, serum sickness) is the prototype small vessel vasculitis. Small venules are affected and the clinical features include palpable purpura, hematuria and abdominal pain.
- Severe systemic necrotising vasculitis (polyarteritis nodosa PAN) is the prototype of a medium vessel vasculitis. Clinical features include fever, abdominal pain, renal involvement (focal segmental glomerulonephritis), and mononeuritis multiplex.
- Giant cell arteritis is a large vessel vasculitis which presents in the elderly with severe headaches and a markedly elevated ESR. Polymyalgia is a frequent accompaniment.
- Laboratory investigations in vasculitis may reveal an elevated ESR, positive HBs Ag (in PAN), anti-neutrophil-cytoplasmic antibodies (in Wegener's granulomatosis), antinuclear antibodies (SLE), positive rheumatoid factor, cryoglobulins (essential mixed cryoglobulinemia) and a variable degree of hypo-complementenemia. Urinalysis may reveal microscopic hematuria.
- Treatment of different vasculitic syndromes varies. Hypersensitivity vasculitis has an excellent prognosis without any specific treatment. Otherwise generally steroids are used initially. Cytotoxic drugs are preferred in patients with PAN and Wegener's granulomatosis.

17.7 Arthritides

Degenerative Joint Disease

Osteoarthritis or degenerative joint disease is a chronic disorder of the predominantly weight bearing joints characterised by degeneration of cartilage and sclerosis of bone at the articular margins. The majority of cases (90 per cent) are classified as primary, that is, without any predisposing cause. Ten per cent of cases are regarded as secondary, and the various causes include congenital defects (hip dysplasia or slipped femoral epiphyses), trauma, metabolic disorders (ochronosis, hemochromatosis, pseudogout and Wilson's disease), and neuropathic joints (also called Charcot's joints, for example, in syringomyelia, diabetes, syphilis).

Pathogenesis In osteoarthritis there is no inflammation of the joint synovium unlike other inflammatory arthritides, and the disorder is one of the articular cartilage and underlying bone. The normal articular cartilage is constantly undergoing a 'damage-repair cycle' due to repetitive microtrauma. In osteoarthritis the proteoglycan concentration of articular cartilage diminishes and the collagen network loosens. This leads to fibrillation of the cartilage and this fissuring is evident as erosions. When a large surface of the articular cartilage is thus eroded, the underlying bone proliferates at the joint margins. This results in osteophyte or spur formation. The underlying bone also shows new bone formation or sclerosis and cystic areas may appear due to the increased transmission of mechanical forces without the buffering elasti cartilage.

Clinical features The most common presentin symptoms in patients with osteoarthritis ar pain, stiffness, joint enlargement and limitatio of movement of the weight bearing joints. Th disorder has an insidious onset and is very slowl progressive, without the 'flares' seen i inflammatory arthritis. Joint pain and stiffnes occur more after vigorous activity with little o no pain in the mornings. Joint enlargement feel 'hard' and bony in contrast to the 'spongy feeling of synovial proliferation in inflammator arthritis. Limitation of movement results fro muscle spasm, intraarticular cartilage fragment (so called 'loose bodies') or due to th incongruity of joint surfaces. In the hands, th PIP and DIP joints are typically involved whil the metacarpophalangeal joints are spared.

Investigation The diagnosis of osteoarthritis i confirmed by the radiological presence of fou cardinal features osteophytes, juxta-articula sclerosis (also termed *eburnation*), loss of join space and subchondral bone cysts.

Management The treatment involves judiciou rest to the joint, reduction in weight (tha reduces the stress on the joints) and the use o analgesics (salicylates or other non-steroidal anti inflammatory drugs). Daily stretching exercise are important. For severe debilitating disease o a single joint, surgical measures may be sough

ıch as total hip replacement for osteoarthritis f the hip.

Rheumatoid Arthritis

Rheumatoid arthritis is a persistent symmetrical nd/or seropositive polyarthritis of unknown tiology. The term seropositive refers to the resence of the rheumatoid factor in serum (of ne patient). For uniformity in the diagnosis of atients for epidemiologic and other studies, a et of criteria has been recommended by the American College of Rheumatology for Disease Diagnosis (Table 17.9).

Table 17.9 Criteria for rheumatoid arthritis

1. morning stiffness (≥1 hr)
2. arthritis of three or more joints
3. arthritis of hand joints (PIP, MCP or wrist)
4. symmetric arthritis
5. subcutaneous nodules
6. serum rheumatoid factor
7. erosions and/or periarticular osteopenia, in hands or wrist joints, seen on X-ray

Criteria 1–4 must be present continuously for six weeks and be verified by a physician. A diagnosis of rheumatoid arthritis requires that at least four of seven criteria are met.

Epidemiology Rheumatoid arthritis is a disease of women of the child bearing age (F:M = 3:1). There is an increased prevalence of the alloantigens HLA DW4 and HLA DR4 of the major histocompatibility complex in subjects with rheumatoid arthritis.

Etiopathogenesis The initiating event in rheumatoid arthritis is synovitis. In the early stages there is inflammation and proliferation of synovial blood vessel as well as synoviocyte hyperplasia. The cellular infiltrate at this stage includes polymorphonuclear leukocytes and T cells. The polymorphonuclear leukocytes phagocytose immune complexes in the synovium and release proinflammatory mediators–leukotrienes, free oxygen radicals, prostaglandins which produce swelling and vasodilatation. The synoviocytes elaborate the joint fluid excessively which results in joint effusions. The monokines released by mononuclear cells include interleukin 1 (IL 1). Excess interleukin 1 in the joint fluid interacts with substance P (a neurotransmitter of pain impulses in the nervous system) in the joint fluid and this is perceived as joint pain.

In the chronic stage of the disease the synovium becomes boggy and the cellular infiltrate predominantly mononuclear. This mass of fibroblasts, vascular and inflammatory cells which accumulates at the synovial membrane-articular cartilage border is called *pannus* and it causes erosions of the cartilage and erosion of the underlying bone. Bony erosions arise due to activation of osteoclasts by the locally produced interleukins and prostaglandins.

Other organs are also involved in a 'granulomatous' inflammation—the so-called *rheumatoid nodules* that occur in the heart, lung and brain.

Clinical features Rheumatoid arthritis has an insidious onset in 60–70 per cent of patients. In about 20 per cent of patients the onset is as an acute polyarthritis with systemic symptoms like fever, weight loss and malaise. After onset, the disease has a variable course—an intermittent course (with remissions and periodic flare-ups), a prolonged remission course or a progressively destructive course (the commonest).

The joints most often involved are the small joints of the hand, particularly the metacarpophalangeal and proximal interphalangeal joints (the distal interphalangeal joints are spared), the wrists, knees and feet. Any joint with synovium can be involved, including the temporomandibular joint, atlantoaxial joint of the cervical spine, hips, shoulders, subtalar joint and sternoclavicular joint. Involvement of the synovium of vocal cord joints (cricoarytenoid

joint) can result in hoarseness. Regional and ethnic differences in manifestations exist. Thus, involvement of the hip joint and the cervical spine is less common in the Indian subcontinent.

With longstanding disease, typical deformities appear—*swan-neck* deformity of fingers (hyperextension at PIP joint with flexion at DIP joints), *button-hole* or *boutonniere* deformity (flexion at PIP joint and extension at DIP joints), and *cock-up* toes (subluxation of heads of metatarsals). Chronic involvement of the wrist leads to rotation of the carpal bones with radial deviation. The fingers compensate with an 'ulnar drift' which is exacerbated by intrinsic muscle spasm.

Subcutaneous nodules are the most common extraarticular manifestation of rheumatoid arthritis and are found in 20–25 per cent patients. Other extraarticular manifestations are shown in Table 17.10.

Investigations The rheumatoid factor is found in 70–80 per cent of patients with rheumatoid arthritis but is not specific. Its presence in the setting of a chronic inflammatory polyarthritis, however, suggests the possibility of rheumatoid arthritis. ANA are found in a fourth of the patients. The ESR is non-specific but helps in assessing disease activity especially when clinical signs are less clear cut. The X-ray features have been mentioned earlier but usually require six months of active synovitis before becoming evident.

Table 17.10 Extraarticular manifestations of rheumatoid arthritis

Ophthalmic
scleritis
episcleritis
sicca syndrome
Pulmonary
rheumatoid nodule
fibrosis
Cardiac
valvulitis (with nodules)
pericarditis
aortitis
Hematologic
lymphadenopathy
Felty syndrome (splenomegaly, leukopenia, RA)
Neurologic
peripheral neuropathy
Skin
subcutaneous nodules
Metabolic
amyloidosis

Management Recent trends in our understanding of rheumatoid arthritis as a persistent immunoinflammatory disease has led to a change from the earlier 'stepped care' or 'pyramidal approach 'in which an initial trial of antiinflammatory analgesic drugs (Table 17.11) was given followed by use of other drugs if symptoms persisted. These other drugs are the *disease-modifying antirheumatic drugs (DMARDs),* also sometimes called the *slow-acting antirheumatic drugs* (*SAARD*).

Present-day treatment emphasises the early use of DMARDs in an attempt to control progression of disease and to modify its natural history. The aims of treatment are to provide symptomatic relief, control the progression of disease and to provide rehabilitation in subjects with deforming disease. The non-steroidal antiinflammatory drugs provide relief of symptoms. There are no important differences in efficacy between one class of NSAID and another but there is a marked interindividual variation in efficacy. The patients can, therefore, be given 4–5 drugs by rotation and they can choose the one that they find most effective and least toxic.

Apart from NSAIDs other drugs which are useful are antidepressant drugs which are also skeletal muscle relaxants. Thus, doxepin and amitryptyline break the *pain→spasm→pain* cycle and simultaneously elevate mood.

The disease-modifying antirheumatic drugs are given early in the disease once the diagnosis is certain. Upto 70–80 per cent of patients will go

Table 17.11 Non-steroidal antiinflammatory drug

Generic name	*Dose*
A. Salicylates	
• aspirin	650–1300 mg q 4–6 hrs
• choline magnesium trisalicylate	1000–1250 mg bid
B. Pyrazole derivative	
• phenylbutazone	100 mg tid
C. Indene derivatives	
• indomethacin	25 mg tid
• sulindac	150–200 bid
• tolmetin sodium	400 mg tid
D. Propionic acid derivatives	
• fenoprofen	300–600 mg qid
• flurbiprofen	50–100 mg tid
• ibuprofen	400 mg qid
• ketoprofen	75 mg tid
• naproxen	250–500 mg bid
E. Fenamic acid derivatives	
• meclofenate sodium	50 mg tid
F. Oxicams	
• piroxicam	20 mg qid
G. Acetic acid derivatives	
• diclofenac sodium	50–75 mg bid

to remission (Table 17.12) with the use of any ne of these drugs. It may take upto three onths for any of these drugs to be effective and e drugs may have to be continued thereafter o. The choice of the initial agent is empirical nless specific contraindications present in a tient make the use of a particular drug zardous.

Intraarticular steroids can provide relief in sabling monoarthritis. Systemic steroids have a le in severe, disabling polyarticular disease fractory to other medication, and in the anagement of associated vasculitis. Along-th drug treatment, rehabilitation measures e non-weight bearing isometric contraction ercises are initiated.

Seronegative Spondyloarthritis Syndrome

ne seronegative spondyloarthropathies are a terogeneous group of disorders which have certain features in common such as, the absence of rheumatoid factor in serum (hence seronegative) prominent involvement of the spine (sacroiliitis or spondylitis), an asymmetric peripheral arthritis (usually below the hip), dominant male involvement, prominent enthesopathic symptoms (heel pain, plantar pain) and a variable association with HLA B27. The disorders include ankylosing spondylitis, Reiter syndrome, reactive arthritis, psoriatic arthritis and enteric arthropathy, associated with inflammatory bowel disease.

Etiopathogenesis The basic pathologic lesion in the SSA syndrome is an *enthesopathy*, that is, an inflammation occurring at the site of insertion of ligaments and tendon to bones (also called insertion tendonitis). Microscopically, the inflammation is indistinguishable from rheumatoid synovitis.

The sequence of events is probably triggered by an environmental agent which is recognised by T cytotoxic cells and inflammation ensues. The process is aided and amplified by the presence of HLA B27 alloantigen. The HLA B27 molecule may act as a receptor for the environmental agent and is in turn recognised by the T cell receptor on a class I restricted CD_8 positive T cell (see earlier section for the explanation of MHC restriction). An alternative explanation is that of *molecular mimicry.* The environmental agent resembles the HLA B27 molecule to such an extent that it is not recognised as foreign and therefore no immune response is mounted and an unchecked disease process results. It is interesting in this regard that proteins of the *Klebsiella* species have been shown to have regions identical to certain parts of the HLA B27 molecule.

Clinical features The patient with *ankylosing spondylitis* presents with low back pain and stiffness which is typically worse after prolonged inactivity, improved by physical activity and not particularly helped by bed rest. Low back pain is

Table 17.12 Disease-modifying antirheumatic drugs

Class	*Dose*	*Side effects*
1. Gold salts		
a. Parenteral gold Myochrysine	50 mg i.m. weekly to a maximum cumulative dose 1000 mg	dermatitis, nephropathy, thrombocytopenia,
b. Oral gold (Auranofin)	3 mg bid	leukopenia, GI side effects with oral gold
2. D–Penicillamine	250 mg morning dose on empty stomach, increase till daily dose 1000 mg	rash, proteinuria, leukopenia, thrombocytopenia, dysgeusia (alteration of taste)
3. Hydroxychloroquine	200 mg p.o. bid	allergic skin reactions, retinal toxicity
4. Immunosuppressive Methotrexate	7.5–10 mg once weekly	GI toxicity, bone marrow toxicity; most important second-line drug
Azathioprine	1.5 mg/kg/day	similar
5. Sulfasalazine	0.5 g p.o. bid	skin rash, headache, hypersensitivity reaction

Table 17.13 Criteria for disease remission (rheumatoid arthritis)

1. morning stiffness less than 15 minutes
2. no fatigue
3. no joint pain
4. no joint tenderness or pain on movement
5. no soft tissue swelling in joints or tendon sheaths
6. ESR (Westergren) < 30 mm/hour in women or < 20 mm/hour in men

At least five criteria must be present for at least two consecutive months.

due to sacroiliitis and stiffness of the back is due to a bony ankylosis that sets in. Peripheral arthritis tends to be oligoarticular, asymmetric with predominant involvement of the distal interphalangeal joints. The swollen digits appear like 'sausage digits'. Systemic involvement may occur and is different from the extraarticular manifestations of rheumatoid arthritis—ocular involvement with anterior uveitis, cardiovascular involvement in the form of inflammation of the aortic root (aortitis with consequent aortic regurgitation), bilateral upper lobe pulmonary fibrosis and genitourinary involvement (prostatitis). Radicular symptoms due to the compression of the roots of the cauda equina by bony prominences may occur late in the disease.

Reiter syndrome is the clinical tetrad of arthritis, urethritis, conjunctivitis and mucocutaneous lesions. Two types of mucocutaneous lesions are unique to this disorder; one is a painless inflammation of the glans penis with the appearance of a circular lesion called *circinate balanitis*, and the other is an exudative exfoliative skin lesion which is seen on the soles of feet and palms and is known as *keratoderma blenorrhagica*.

Reactive arthritis follows an episode of urethritis (urethritic form) or a diarrheal or dysenteric illness (enterocolitic form).

Psoriatic arthritis usually occurs in the setting of severe cutaneous disease but it can on occasion antedate the skin involvement. Pitting of the nails and distal interphalangeal joint involvement are typical.

A comparison of some of the spondyloarthropathies is shown in Table 17.14.

Investigations X-ray of the sacroiliac joints (AP and oblique veiws) and the spine can help substantiate sacroiliiitis – blurring, irregularity of joint margins, periarticular sclerosis, erosions and narrowing of joint spaces being prominent. Testing for sacroiliitis is also done clinically by checking for tenderness on compression of the joints. *Schober's test* is a measure of mobility of the lumbar spine. It measures the difference in distance between the line connecting the posterior iliac spines and a point 10 cm vertically above along the spine when the patient is erect and with maximum forward flexion. With forward flexion the original 10 cm must increase by over 5 cm in the presence of the normal mobility. An increase of less than 5 cm suggests limited mobility. Similarly, chest expansion is measured to check mobility of costovertebral joints. Normal chest expansion must be more than 5 cm measured from full expiration to full inspiration.

Management Apart from psoriatic arthritis for which specific therapy exists, the management of other forms of spondyloarthropathies is symptomatic. Among the NSAIDs, the indole-related drugs seem to provide most relief (indomethacin, tolmetin and phenylbutazone). Exercises like swimming and spinal extension exercises and physiotherpy have been found to be beneficial. For psoriatic arthritis, methotrexate is the treatment of choice.

CRYSTAL-INDUCED ARTHROPATHIES

Crystal-induced arthropathies are a group of diseases caused by the deposition of various crystals in the joint space which in turn initiate synovial inflammation. When the deposited crystals are of monosodium urate, the disorder is gout; when calcium pyrophosphate crystals are

Table 17.14 A comparison of spondyloarthropathies

	Ankylosing spondylitis	*Reiter syndrome*	*Reactive arthritis*	*Psoriatic arthritis*
1. sex	M>F	M=F	M>F	F>M
2. HLA B27+ve	95%	80%	80%	20%
3. spine involvement with ankylosis	+	–	–	–
4. peripheral arthritis	lower extremity more common	lower extremity more common	lower extremity	upper extremity, distal inter-phalangeal joints
5. mucocutaneous lesions	–	+ balanitis circinata and keratoderma blenorrhagica characteristic	–	+ may exist without skin disease
6. nail involvement	–	–	–	+ (pitting)
7. ocular involvement	uveitis	conjunctivitis	–	uveitis

deposited, the disease is called *pseudogout. Hydroxyapatite crystal disease* is the third type of disorder in this category.

Epidemiology Gout is a disease of middle-aged men whereas pseudogout usually causes an asymptomatic illness in the elderly. Hydroxyapatite crystal disease occurs when the serum calcium and phosphorus product is elevated, and occurs, mostly in patients with renal failure.

Gout

Etiology Gout is a disorder of purine metabolism characterised by hyperuricemia (serum uric acid >7 mg/dl in men, >6 mg/dl in women) and urate deposition in tissues. Ninety per cent of subjects with gout are *underexcreters* of uric acid that is, they excrete less than 700 mg of uric acid daily in urine. This underexcretion is most often idiopathic but can occur in renal disease (chronic renal failure), lead poisoning, the use of drugs (thiazide, diuretics, alcohol) or toxemia of pregnancy. Ten per cent of subjects are *overproducers*, that is, they excrete more than 750–1000 mg of uric acid in urine per 24 hours. Causes of such overproduction include inherited enzyme deficiencies of purine metabolism (hypoxanthine guanine phosphoribosyl transferase — HGPRT deficiency) or increased turnover of nucleic acids (myeloproliferative disorders, lymphoproliferative disorders, hemoglobinopathies).

Pathophysiology and clinical features Four stages of gout exist—asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout and chronic tophaceous gout. *Asymptomatic hyperuricemia* is the initial phase which lasts for about 20–30 years. *Acute gouty arthritis* is the primary clinical manifestation of gout. It is typically a monoarthritis of a distal joint of the lower extremity, the big toe being the site in over 50 per cent (the attack is then described as *podagra*). The pain is intense and debilitating till it resolves over a few days. It is related to release of inflammatory mediators and lysosomal enzymes of neutrophils which have engulfed the uric acid crystals. The acute attack is followed by another asymptomatic period, the *intercritical phase* which usually lasts upto a year before arthritis recurs. Subsequent attacks tend to be polyarticular, more severe and of longer duration. If left untreated, after 10–20 years of further urate deposition, *chronic tophaceous gout* develops. A *tophus* is a collection of urate crystals surrounded by inflammation, cells and fibrosis. Tophi are most commonly formed on the helix or antihelix of the ear but may also occur on the Achilles tendon or over the olecranon process.

Renal involvement may develop at any time during the course of gout and takes the form of nephrolithiasis with or without obstructive uropathy.

Diagnosis The demonstration of needle-shaped, negatively birefringent crystals (in polarised light) in the joint fluid is diagnostic. Negative birefringence means taking on the colour of the background (i.e. yellow) when the long axis of the crystals is parallel to the axis of the polariser and analyser of the microscope. Calcium pyrophosphate crystals are positively birefringent, that is, appear blue in the direction; urates are yellow.

Management Acute attack: The drug of choice for an acute attack is non-steroidal anti-inflammatory drug (indomethacin 50 mg every six hours tapered with clinical response). Colchicine (0.6 mg orally every hour till pain relief) is also highly effective but treatment is associated with significant gastric intolerance.

Both drugs can also be used subsequently for prophylaxis of further acute attacks (colchicine 0.6 mg tds or indomethacin 25 mg bid)

Antihyperuricemic therapy: Drugs which lower serum uric acid levels are indicated in patients who have had more than two attacks in a year, have visible tophi, joint deformity or

radiologic evidence of joint damage or renal dysfunction.

These drugs belong to two categories: drugs that enhance uric acid excretion by the kidneys-'uricosuric' agents, and drugs that decrease uric acid production.

Uricosuric drugs include probenecid (0.25 g – 1 g bid) or sulfinpyrazone (50 mg tid increased upto 800 mg/day). They are avoided in the presence of nephrolithiasis or renal dysfunction or if the urinary excretion of uric acid is greater than 1000 mg/day. In these cases, allopurinol, a xanthine oxidase inhibitor that decreases uric acid production, is administered. Allopurinol is started in a dose of 100 mg/day and the dose increased at weekly intervals so as to maintain serum uric acid levels below 6 mg/dl. It must be borne in mind that in the first few months of antihyperuricemic therapy, serum uric acid levels must be frequently monitored and antiinflammatory drugs (NSAIDs or colchicine) should be given concomitantly otherwise an acute attack may be precipitated. A high fluid intake and alkalinisation of urine is recommended for patients with gouty nephropathy.

KEY CONCEPTS

Rheumatoid arthritis

- RA is a chronic inflammatory symmetrical erosive polyarthritis which is associated with systemic features and the presence of circulating anti-IgG antibodies (rheumatoid arthritis). There is an association with HLA D4 and DR4.
- Pathologic features include a synovitis with formation of granulation tissue (pannus) which destroys articular cartilage and subchondral bone (erosions); this results in fibrosis, ankylosis and joint effusions.
- Clinically, RA presents with joint pains, joint swelling and stiffness. Stiffness is worse in the mornings and improves with activity. Joints which are typically affected include the wrists, hands (sparing the DIP), knees, ankles, the temporomandibular joint and the cervical spine. Joint deformities are characteristic (swan-neck, button-hole). Systemic features include subcutaneous nodules, vasculitis, splenomegaly (Felty syndrome), pericarditis, mononeuritis and episcleritis.
- Laboratory investigations reveal elevated ESR and CRP in the acute phase. Rheumatoid factor is positive in over three-quarters. Radiologic features include marginal erosions, reduction in joint space and periarticular osteoporosis.
- Management includes physiotherapy, occupational therapy and medical therapy to relieve symptoms and control disease activity. NSAIDs are useful for symptomatic relief but do not modify the course of the disease. For this purpose the disease-modifying antirheumatic drugs (sulfasalazine, gold, hydroxychloroquine, methotrexate and d-penicillamine) are useful. Intraarticular steroids can provide relief in disabling monoarthritis, while systemic steroids have a role in refractory disease with considerable polyarticular disability, and in RA with vasculitis.

Seronegative spondyloarthropathies

- This is a group of inflammatory arthritides characterised by prominent involvement of the axial skeleton (sacroilitis), an asymmetric oligoarticular peripheral arthritis (below hip) and enthesopathy (insertion tendonitis). There is a variable association with HLA B-27 and a male predominance. The radiologic hallmark is persistent new bone formation at sites of enthesitis.
- Ankylosing spondylitis presents with low backache and young adults are affected. Extraarticular features include anterior uveitis, aortitis (with aortic regurgitation), apical pulmonary fibrosis and a cauda equina syndrome. The radiologic hallmark is a *bamboo spine*, and syndesmophytes.
- Reiter syndrome is characterised by the tetrad of arthritis, urethritis, mucocutaneous involvement and conjunctivitis. There may be a preceding history of urethritis or a dysenteric illness and there is a male predominance. Heel pain is a common symptom. Typical mucocutaneous manifestations include *circinate balanitis* and *keratoderma blenorrhagica*.
- Psoriatic arthritis usually follows the skin manifestations of psoriasis. Involvement of the DIP joint and the pitting of nails suggest the diagnosis.

➢ NSAIDs are the mainstay of medical treatment of the SSA syndromes. Psoriatic arthritis is treated with methotrexate or sulfasalazine.

Osteoarthritis

➢ OA is characterised by destruction of articular cartilage, presumably due to wear and tear (fatigue fractures of collagen and subchondral bone). The end result is loss of normal joint function.

➢ OA increases with age. It may be primary (idiopathic) or secondary (e.g., trauma, endocrine disease [acromegaly, Cushing's disease]).

➢ Clinical presentation is with pain and swelling of the joints which is more on activity and is relieved with rest (to the joint). The involved joints are stiff and there is a variable degree of loss of movement. Weight-bearing joints are preferentially involved (hips, knees, spine, and hands). Bony deformities may appear (Heberden nodes on the dorsal aspect of the DIP and Bouchard nodes on the PIP).

➢ Laboratory investigations usually reveal a normal ESR. The radiologic features include prominent osteophytes and narrowing of the joint spaces.

➢ Treatment includes rest to the joint, weight reduction, regularising exercise, physiotherapy, and NSAIDs (for pain relief).

Gout

➢ Gout is a condition characterised by hyperuricemia and deposition of uric acid crystals in and around joints (gouty arthritis) and in the kidneys (urolithiasis).

➢ Gout can be due to *overproduction* of uric acid (<10%; hematologic malignancies, ethanol intake, glycogen storage disease), or it may result from *underexcretion* of uric acid (90%)-increased tubular secretion or reabsorption.

➢ Gout occurs typically in middle-aged males and the first metacarpophalangeal joint is often affected initially (*podagra*). The joint is inflamed and exquisitely tender. Chronic gout results in deposition of uric acid (*tophi*) and joint destruction. Renal involvement may occur due to the formation of uric acid stones or due to urate deposition in the medullary interstitium.

➢ The diagnosis is suspected if the serum uric acid is elevated (>7 mg/dl in men and >6 mg/dl in women). Arthocentesis with examination of the aspirated fluid under polarized light is confirmatory if needle-shaped negatively birefringent crystals of sodium urate are seen.

➢ An acute attack of gout is best treated with indomethacin or colchicine. Treatment of chronic gout includes high fluid intake, low purine diet, alkalinisation of urine, uricosuric drugs (probenecid) and administration of allopurinol (xanthine oxidase inhibitor). Abstinence from alcohol and weight reduction are useful adjunctive measures.

17.8 Amyloidosis

Amyloid is a complex protein formed and deposited in tissues in certain disease states. Amyloidosis is the state in which amyloid deposits in various organs with or without clinical dysfunction.

Pathogenesis Amyloid is a protein which, though amorphous under the light microscope, is actually a complex of two components. One of the components is a non-branching fibrillar protein which is heterogeneous (depending on the underlying etiology) and the other is a pentagonal unit identical with a serum alpha globulin (called serum amyloid precursor or SAP) which is common to all forms of amyloid. Though the fibrillar component varies in its exact chemical composition (as several different proteins are capable of forming amyloid fibrils), each of the proteins has a β pleated configuration. This molecular structure accounts for the aggregation of insoluble protein crystalloids. The structure is also responsible for the 'Congo red staining' of amyloid as well as for the 'apple green birefringence' under polarised light. A classification of amyloidosis is shown in Table 17.15.

In *light chain amyloidosis,* the protein which deposits is a fragment of a monoclonal immunoglobulin containing the 'variable portion of the light chain'. It complicates about five per cent of cases of multiple myeloma. Most commonly there is no underlying cause. This condition is known as primary light chain amyloidosis.

Table 17.15 Types of amyloidosis

1. Light chain amyloidosis
   a. with multiple myeloma
   b. without myeloma i.e. primary
2. Protein A amyloidosis
   i. chronic infections
      - osteomyelitis
      - leprosy
      - tuberculosis
   ii. chronic inflammatory arthritis
      - ankylosing spondylitis
      - rheumatoid arthritis
   iii. Familial Mediterranean Fever
3. Heredofamilial amyloidosis
4. Localised organ amyloidosis

The causes of *protein A amyloidosis* are also shown in Table 17.15. As the name suggests, the principal component of the amyloid in this condition is a protein called 'A' protein related to a serum high density apolipoprotein - 'SAA' (serum amyloid A) protein. Possibly chronic immunoinflammation in these disorders leads to excess hepatic synthesis of SAA (under the influence of elevated levels of monokines like IL-1) which in turn is partly degraded by the mononuclear cells to form 'AA'.

In *heredofamilial amyloidosis* the protein deposited is *transthyretin* (pre-albumin) which differs from the normal transthyretin by virtue of a single amino acid substitution.

In *localised organ amyloidosis* the nature of the deposited protein varies with the tissue where it is found, such as, thyroid (calcitonin precursor), heart (atrial natriuretic factor) and brain (beta protein A4)

Clinical features (Fig 17.9)

Light chain amyloidosis

In this disorder any organ other than the brain and the spinal cord can be affected. Mucocutaneous involvement is not uncommon. The tongue is typically large (macroglossia) and has restricted mobility. Cutaneous lesions take the form of small yellow-orange subepithelial nodules on the face and axilla or of 'pinch purpura' (purpuric lesions appear if the skin is pinched indicating 'fragile' blood vessels). Deposits in the iris of the eye result in irregular pupils and deposits in the lacrimal and salivary glands may render them rubbery and palpable. Hoarseness may result from laryngeal involvement. Cardiovascular involvement is

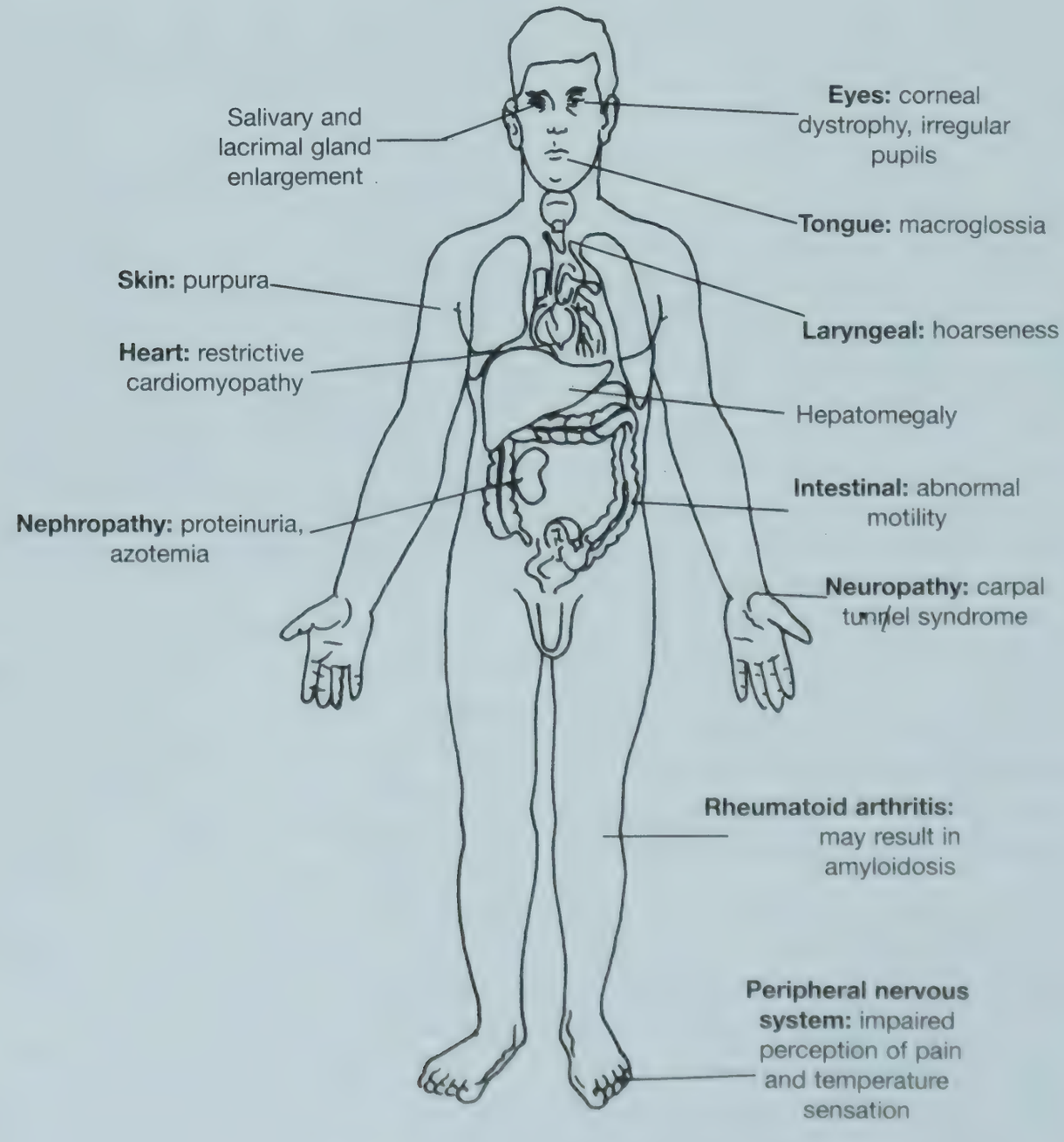


Fig 17.9 Clinical features of amyloidosis

een in a fourth of patients and takes the form of ongestive heart failure resulting from a restrictive' cardiomyopathy (see earlier ection). Pedal edema and orthostatic hypo-ension are common. Involvement of the kidneys ypically results in isolated non-nephrotic roteinuria with some degree of azotemia. Hepatomegaly is seen in roughly 50 per cent of atients and motility abnormalities of the ntestines (due to involvement of the muscularis ayer) can result in constipation, diarrhea or a malabsorption syndrome. Peripheral nervous ystem involvement (15 per cent) results in a olyneuropathy (axonal type, see earlier ection) or a compressive mononeuropathy carpal tunnel syndrome).

The major morbidity and mortality in AL amyloidosis results from cardiac involvement with progressive cardiac failure and sudden arrhythmias.

Rectal biopsies or skin biopsies may help to establish the diagnosis (sensitivity of 65 per cent and 45 per cent, respectively). Aspiration of abdominal fat pad has emerged as a procedure with a high diagnostic yield.

Protein 'A' amyloidosis

The features of the specific underlying disorder are obvious in the patients. A majority of patients present with renal involvement chiefly in the form of a 'nephrotic range' proteinuria with azotemia.

A few patients present with hepatosplenomegaly or the carpal tunnel syndrome. Involvement of other organ systems is uncommon.

Rectal biopsy is positive in about 65 per cent of cases. Though renal biopsy has a higher yield, it also entails a higher risk of bleeding complications.

Heredofamilial amyloidosis

Several types are described based on disease peculiarities in different populations. Most involve the peripheral nervous system with a chronic sensorimotor polyneuropathy (of an axonal type). Bladder and bowel disturbances occur occasionally. Cardiac and cutaneous involvement is less severe than in AL amyloidosis.

Localised organ amyloidosis

This is usually asymptomatic and is discovered only at autopsy.

Treatment There is no specific treatment for amyloidosis. Colchicine, however, has been found to be effective in Familial Mediterranean Fever. Combinations of prednisolone, melphalan and colchicine have been tried with variable results. Similarly, use of the agent dimethyl sulphoxide has also shown variable results. Renal transplantation can be used in carefully selected patients with severe renal amyloidosis and end stage renal disease. Digitalis should be used with care in amyloid heart disease.

KEY CONCEPTS

- This is a group of disorders characterised by deposition of a fibrillar eosinophilic material (with a β pleated structure) in the tissues.
- Causes of amyloidosis include multiple myeloma (AL fibrils; Ig light chains), chronic inflammation (rheumatoid arthritis, bronchiectasis, leprosy; AA fibrils derived from serum precursor SAA), Familial Mediterranean Fever (AA fibrils), senile changes (cardiac deposition of AS fibril; prealbumin) and MEN syndromes (calcitonin precursor; AEmct fibrils).
- Clinical features include macroglossia, pinch purpura, hepatosplenomegaly, malabsorption syndrome, cardiomyopathy, peripheral neuropathy (including entrapment neuropathies), nephrotic syndrome and chronic polyarthritis.
- The diagnosis is made with either a tissue biopsy (usually rectal biopsy) or by aspiration of the abdominal fat pad; apple-green birefringence on Congo red staining is diagnostic. Urinalysis reveals proteinuria.
- Treatment is symptomatic. Colchicine has a role in treatment of Familial Mediterranean Fever.

17.9 Sarcoidosis

Sarcoidosis is a disorder characterised by a heightened immune response to an as yet unidentified antigen resulting in the formation of non-caseating granulomas throughout various organs.

Epidemiology There is considerable geographic heterogeneity in the worldwide prevalence rates of sarcoidosis with a high prevalence rate in the west and lower prevalence in the east. The prevalence is higher in the negroid race as compared to the caucasoid race. The disease occurs most often in young adults and in non-smokers.

Etiopathogenesis and pathology The study of bronchoalveolar lavage fluid in subjects with pulmonary involvement has helped clarify certain aspects of the immunopathogenesis of the disease. An unknown antigen presumably activates alveolar macrophages and helper-inducer T lymphocytes. The activated T lymphocytes release monokines which attract blood monocytes. The T lymphocytes also induce a non-specific polyclonal proliferation of B cells which accounts for the hyperglobulinemia seen in this disorder. Pulmonary B lymphocytes are also activated to differentiate into mature plasma cells. The granulomas formed consist of a core of epitheloid cells, a surrounding layer of giant cells (with or without inclusions) and a peripheral cuff of mononuclear cells. The granulomas are 'non-caseating' or '*hard*', a feature that enables a distinction from the 'caseating' or 'soft' granulomas of tuberculosis.

The clinical features of sarcoidosis are due to organ involvement by granulomata resulting in dysfunction of the organ.

Clinical features Ninety per cent of patients with sarcoidosis have pulmonary involvement. Symptoms are, however, present in only 60 per cent and are dependent on the extent of pulmonary involvement (Fig 17.10). Patients with bihilar adenopathy are most often asymptomatic and frequently undergo spontaneous remission. Patients with parenchymal involvement have pulmonary symptoms, chiefly dyspnea and cough. Pleural involvement is rare.

Constitutional symptoms such as fever, anorexia and weight loss occur in a third of patients. Sometimes sarcoidosis can present acutely in one of two forms: 1) with erythema nodosum, arthralgias and bihilar adenopathy (the so-called *Lofgren syndrome*), or 2) with fever, parotid enlargement, anterior uveitis and facial nerve palsy (*Heerfordt syndrome*).

Hepatic involvement is common (70–90 per cent) and is typically benign and asymptomatic. An elevated alkaline phosphatase level in serum (due to intrahepatic cholestasis induced by periportal granulomata) is the usual manifestation. Other organ systems which are commonly involved include lymph nodes (70 per cent), eye (25 per cent) and the skin (20 per cent). Apart from bihilar lymphadenopathy

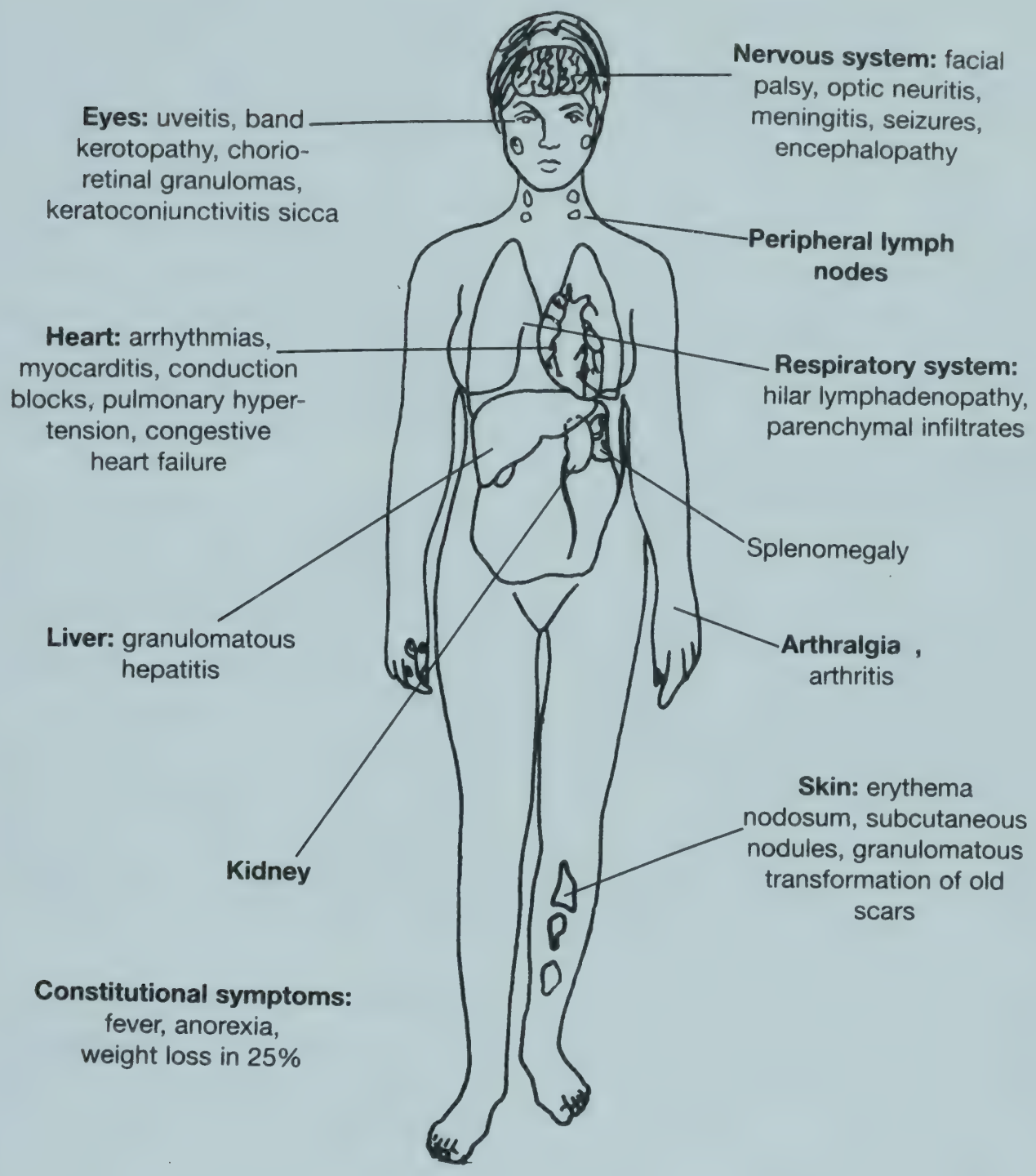


Fig 17.10 Clinical features of sarcoidosis

vhich is the diagnostic hallmark of sarcoidosis), peripheral lymphadenopathy characterised by on-adherent, firm, painless cervical, axillary id epitrochlear nodes are often encounted. cular involvement is typically in the form of an terior uveitis with blurred vision, photophobia id tearing. On occasion there may be posterior veitis, corneal involvement in the form of a *ınd keratopathy* (hypercalcemia-related) or crimal gland involvement with dry, sore eyes eratoconjunctivitis sicca or simply 'sicca' syndrome). Skin involvement is most often as erythema nodosum, that is, bilateral tender red nodules on the anterior aspects of the legs. Plaque-like skin lesions may occur on the face and buttocks whereas subcutaneous nodules may arise over the trunk. An uncommon destructive lesion is '*lupus pernio*' — indurated, chronic, blue-purple, shiny lesions on the nose, cheeks and lips. Organ sytems that are less frequently involved include the heart (five per cent), the nervous system (five per cent) and the

musculoskeletal system (five per cent). Cardiac involvement is primarily in the form of ventricular tachyarrhythmias and bradyarrhythmias (like complete heart block) due to the tendency of granulomata to involve the conduction system. The nervous system involvement is most often as a sudden-onset, unilateral facial nerve palsy that is transient. Optic nerve involvement is next in frequency. Hypothalamic involvement can result in a central diabetes insipidus. The musculoskeletal system is also occasionally involved manifesting as large joint arthritis or arthralgias and tender painful cystic lesions involving the small bones of hands and feet.

Diagnosis and clinical investigations Abnormalities evident on laboratory investigations include a lymphocytopenia, hyperglobulinemia, elevated levels of the serum angiotensin converting enzyme (SACE) and, in rare cases, hypercalcemia. Hypercalcemia results from an increased absorption of calcium from the intestines consequent to elevated levels of 1, 25 dihydroxy vitamin D, produced by mononuclear cells in the granulomas. The enzyme SACE is produced from both pulmonary endothelial cells as well as epitheloid cells in the granulomas. The immune dysfunction can result in cutaneous anergy in upto 60 per cent of patients. The roentgenologic staging and features are depicted in Fig 17.11. Pulmonary function tests reveal restrictive ventilatory dysfunction and BAL fluid shows a lymphocytic alveolitis. Transbronchial pulmonary biopsy has a high diagnostic yield. The radionuclide gallium-67 scans will result in concentration of radioactivity in the activated alveolar macrophages (which take up the radioisotope) in pulmonary regions with inflammatory alveolitis and in the lacrimal glands, parotid glands and hilar nodes. The test is, however, neither diagnostic nor of prognostic value.

The diagnosis is, therefore, established by the demonstration of typical non-caseating granulomata on tissue biopsy. It is, however, mandatory to rule out infectious agents like mycobacteria or fungi with specific stains and culture of tissue material.

Natural history Whereas sarcoid disease tends to regress spontaneously within two years in most patients, it can be progressive in upto 20 per cent of patients, and results in respiratory failure in five per cent.

Treatment Glucocorticoids are the agents of choice in treating sarcoidosis. They suppress the activated T helper-inducer lymphocytes and suppress granuloma formation in organs. They

Stage 1
(Hilar adenopathy)
40–60%

Stage 2
(Hilar adenopathy+
parenchymal
infiltrates)
25–35%

Stage 3
(Parenchymal
infiltrates)
5–15%

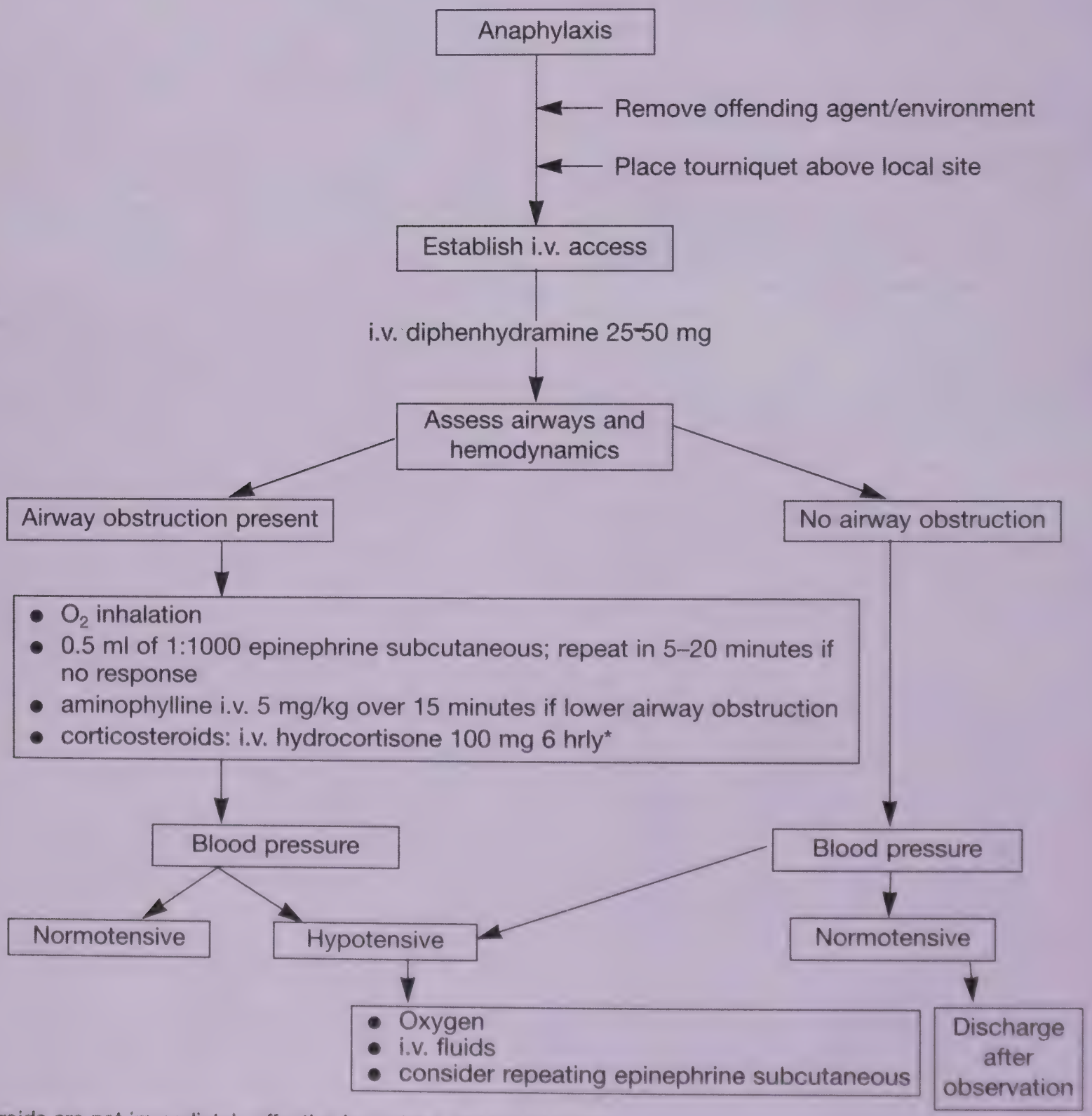
Fig 17.11 Staging of sarcoidosis based on X-ray features

re, however, not indicated in all subjects, given ne excellent natural history of the disease in the najority of patients. They are used if there is cular involvement (uveitis), greater than tage I pulmonary disease, cardiac or nervous system involvement, hypercalcemia, painful bony cysts or disfiguring skin lesions (lupus pernio). A dose of 1 mg/kg of prednisolone for six weeks which is subsequently tapered over 12 weeks is usually sufficient.

KEY CONCEPTS

- Sarcoidosis is a chronic granulomatous disease of unknown etiology. Young adults are affected most often and present with symptoms resulting from the granulomatous infiltration of the various organs involved.
- The lungs are involved in over 90 per cent of patients. Bihilar lymphadenopathy is the hallmark and parenchymal involvement results in progressive interstitial fibrosis. Skin involvement may present as erythema nodosum (*Lofgren syndrome*), as subcutaneous nodules or as lupus pernio (indurated, blue destructive lesions on the face). The eyes may be involved: a granulomatous uveitis, band keratopathy and lacrimal gland enlargement may result. Hepatic sarcoidosis manifests as elevation of ALP levels. Neurosarcoidosis is often asymptomatic. Manifestations include facial nerve palsy (*Heerfordt syndrome*), a basilar meningitis or hypothalamic-hypophyseal lesions. Myocardial involvement results in arrhythmias and conduction system disturbances.
- The diagnostic hallmark of sarcoidosis is the demonstration in tissues of a non-caseating granuloma. The ESR may be elevated and there may be eosinophilia with a monocytosis. The chest X-ray reveals bihilar lymphadenopathy and the pulmonary function tests show a restrictive defect. Broncho-alveolar lavage cytology demonstrates a lymphocyte predominance. The serum SACE levels are high and there is hypercalcemia and hypercalciuria.
- Asymptomatic patients need not be treated. Symptomatic patients may benefit from a 3-6 month course of steroids. Chloroquine, azathioprine and methotrexate are useful adjuncts to steroids. Prognosis is generally good unless there is extensive pulmonary fibrosis.

17.10 Immunoinflammatory emergency



* Steroids are not immediately effective but take a few hours to act.

18

Poisoning and Disease due to Environmental Agents

POISONING

Any substance which, when administered in any form, produces ill health, disease or death is a *poison*. Poisoning can be acute or chronic. Acute poisoning is a frequent cause of emergency admissions to the hospital and is associated with considerable morbidity and mortality.

Epidemiology Poisoning may be *suicidal*, *homicidal* or *accidental*. About a fourth of suicide attempts in India are due to consumption of a poisonous substance. There is some regional heterogeneity, with higher rates being reported from the states of West Bengal, Tamil Nadu and Kerala. Accidental poisoning constitutes about five per cent of all countrywide accidental deaths, again with some regional differences. In Tamil Nadu and West Bengal, accidental poisoning constitutes 15–17 per cent of accidental deaths. There is a male preponderance in all types of poisoning. The common poisons in India are insecticide poisoning (organophosphorus, organochlorine and carbamate compounds), copper sulphate poisoning, methanol poisoning, aluminium phosphide poisoning, *datura* poisoning, opiate poisoning and corrosive intake. In south India, insecticide poisoning is the commonest whereas in the northern states of India, aluminium phosphide and copper sulphate poisoning are very common.

Mechanism of action The common mechanisms of action of poisons include : 1) *interaction with key enzymes*. Thus, heavy metals bind to the sulphydryl groups of enzymes. Cyanide and aluminium phosphide bind to cytochrome oxidase thus paralysing the mitochondrial electron transport chain with consequent cessation of cellular respiration. Poisons like organophosphorus derivatives or carbamates can bind to the enzyme acetylcholinesterase. 2) *blockade of specific receptors* like blockade of acetylcholine muscarinic receptors by atropine (active principal of datura) and 3) *conversion to toxic metabolites*: methanol is converted to formaldehyde and formic acid, and ethylene glycol is converted to oxalic acid.

General principles of management The principal aims are to prevent further absorption of the poison, to neutralise whatever poison has been absorbed, and to provide supportive care to the vital systems of the body.

Prevention of further absorption

1. *Gastric aspiration* followed by *lavage*: This method involves the insertion of a large bore gastric tube and lavaging the stomach with lavage fluid. It is contraindicated in the unconscious patient, or when kerosene or any petroleum distillate poisoning is suspected (as there is a risk of aspiration into the lungs), or when some corrosives have been ingested (as there is a risk of perforation of the stomach). It is generally not helpful if more than four hours have elapsed since the ingestion of the poison

except in poisoning due to salicylates, copper sulphate or morphine.

2. *Emesis*: This method is employed for young children, either by the use of ipecac syrup or with the use of apomorphine (0.06–0.1 mg/kg).

3. *Activated charcoal*: This is a safe, effective and inexpensive agent which utilises the principle of *chemoabsorption*. It is efficient because the charcoal particles have extensive internal pores and a large surface area for absorption. The poisons absorbed by activated charcoal include barbiturate, salicylates, digitalis and alcohol. However, DDT, malathion, carbamates, methanol and boric acid are not absorbed by charcoal. Care must be taken not to administer the antidote and charcoal together as the former may also be absorbed by charcoal. The usual adult dosage is 30 g of charcoal orally, repeated every two hours.

Removal of absorbed poison

1. *Altering urine pH* : Most absorbed poisons are excreted through the kidney by glomerular filtration (non-protein-bound fraction) and by active secretion by the proximal convoluted tubule. There is partial reabsorption in the distal convoluted tubule (non-ionic diffusion that is pH dependent). The basic principle is to render the poison into an ionised and, therefore, lipid insoluble form which in turn decreases renal reabsorption resulting ultimately in increased renal excretion. The ionised fraction is increased by altering the urinary pH to approach the *isoelectric pH* (pKa) of the corresponding toxin. Thus, for weakly acidic poisons the urine is alkalinised and for weak bases, the urine is acidified. Usually alkalinisation or acidification is combined with high dose diuretic administration: this is termed *forced diuresis*. Alkalinisation of urine is achieved by infusion of sodium bicarbonate with an attempt to keep urinary pH greater than 7.5. It is useful in salicylate poisoning and in poisoning with long-acting barbiturates. Acidification of urine is useful in poisoning with amphetamine, quinine/quinidine, pethidine or strychnine. It is achieved with oral administration of ammonium chloride (4 grams every two hours) or by the intravenous use of arginine or lysine hydrochloride solution (10 grams). The target urine pH should be 7. Frusemide is the commonly employed diuretic and its dosage is titrated based on the urine output, the target urine output being 6 ml/minute (360 ml/hour).

2. *Hemodialysis*: This is the most effective and rapid method of removing dialysable poisons provided they are not irreversibly bound to tissue proteins. It is useful in treating poisoning due to barbiturates, salicylates, methanol, lithium, bromides and ethylene glycol. It is not useful for digitalis, quinine/quinidine or diazepam poisoning.

3. *Exchange transfusion*: This is usually used in treating poisoning in children due to a non-diffusible, non-dialysable, highly protein-bound toxin.

4. *Newer dialysis methods*: In *lipid dialysis,* lipid is added to the dialysate and this increases the clearance of highly lipid soluble substances. In *albumin dialysis,* albumin is added to the dialysate (for phenobarbiturate and methyl salicylate poisoning).

5. *Hemoperfusion*: In this method, blood is perfused through a column containing activated charcoal or resin. It is simpler, less expensive, provides higher clearance rates and is better for lipid soluble toxins as compared to hemodialysis. It is used for treating barbiturate, glutethimide or paracetamol poisoning.

Neutralisation of poison through antidotes

Antidotes are substances which reverse the manifestations of the poison by binding it reversibly or irreversibly and displacing it from its site of action. Specific antidotes of some poisons are listed in Table 18.1.

Supportive care to vital systems: The arrival of a patient with suspected poisoning should immediately initiate an assessment of vital system functions, that is, cardiorespiratory, renal and cerebral functions. The airway is cleared with suction to remove vomitus, displaced false

teeth or bronchial secretions. The respiratory rate and depth, and the colour of the skin and mucosa are crude guides to the status of ventilation. More objective methods involve the use of a bedside Wright's spirometer. A minute volume less than 4 litres/minute or a tidal volume less than 5 ml/kg signifies respiratory depression. Arterial blood gas analysis can be obtained to further facilitate decision making. Presence of mild hypoxemia (PO_2 60–80 mmHg) and normocapnia (PCO_2 40–50 mmHg) is an indication for oxygen therapy. The presence of severe hypoxemia (PO_2 <60 mmHg) and hypercapnia (PCO_2 >50 mmHg) indicate the need for some form of assisted ventilation. The pH of blood dictates the use of sodium bicarbonate (indicated for severe metabolic acidosis) A pH of pulmonary suction fluid which is less than 3 signifies possible aspiration of gastric contents.

The circulatory system is assessed by careful evaluation of the degree of hydration (dryness of mucosa, skin turgor, jugular veins), the heart rate, blood pressure and skin colour; cutaneous pallor may indicate severe reflex vasoconstriction. Fluid deficits are corrected by volume replacement. A central venous pressure line can be inserted and fluid replacement may be guided to maintain a CVP of 10–14 cm H_2O and to maintain a urine output greater than 0.5 ml/kg/hour. Vasopressors are indicated for refractory hypotension which is non-responsive to fluid replacement. Vasopressors must be used with care because excess splanchnic vasoconstriction can have deleterious effects. Inotropes are indicated for specific myocardial depressant toxins (e.g., aluminium phosphide). Arrhythmias are treated with use of drugs targeted at the specific arrhythmias. Correction of acid-base imbalances (such as metabolic acidosis) may also improve myocardial function.

Clinical Approach to a Patient with Suspected Poisoning

Identification of the substance ingested is of utmost importance in cases of suspected poisoning. Though laboratory identification of the poison is possible by screening blood, urine or gastric aspirate, treatment must be instituted before such results become available. A careful history from the patient's family or friends about the substance ingested and the dosage of the substance is often helpful in providing clues. If a clear-cut syndrome of cholinergic or anticholinergic excess, extrapyramidal signs or sympathomimetic signs are identified, the differential diagnoses can be considered and specific therapy can be initiated.

DISEASES DUE TO ENVIRONMENTAL AGENTS

Electrical Injury

Pathophysiology The main defence mechanism of the body against electrical current is the electrical resistance of the skin. With normal integumentary resistance, a current of 300 mamp can produce ventricular fibrillation. The *fibrillatory potential* of any current is related to the nature of the current, its frequency and its strength. Alternating current is more fibrillatory in comparison to direct current. Cycles with a frequency of less than 60 cycles per second and current strength below 7.5 amp are fibrillatory. Higher current strengths produce cardiac asystole and sustained contraction of the skeletal muscle resulting in respiratory paralysis. A break of skin or moistening of skin can lower the resistance of the integument and can render the subject susceptible to injury at extremely low current levels.

Electrocution related to 'lightning' usually results in respiratory paralysis and cervical vertebral injuries due to a fall.

Management The essence of handling electrical injuries is to prevent them. Proper 'earthing' of equipment significantly reduces injuries as does restriction of the use of external earth wires. Once electrocution has occurred, however, the first step is to interrupt the flow of

Table 18.1 Clinical approach to the diagnosis and management of unknown poisons

Clinical syndrome	*Clinical features*	*Possible agents*	*Antidotes*
1. Cholinergic			
Muscarinic	hypersalivation, hyperlacrimation, diarrhea, bronchorrhea, urinary/ fecal incontinence, miosis, blurred vision, bradycardia, hypotension	organophosphates	Atropine 2 mg i.v. repeat every 15 minutes till atropinisation (dilated pupils, dry mouth)
Nicotinic	fasciculations, muscle weakness	carbamates	Pralidoxime 1 g i.v. over 30 minutes
2. Anticholinergic	dry mouth, blurred vision, tachycardia, hyperthermia, ileus, urinary retention, flushed skin, hallucinations, excitation	datura or belladona alkaloids	Physostigmine 0.5–2 mg i.v./i.m. q $^1/_2$—1 hour
	above + arrhythmias (ventricular and supraventricular tachycardia, conduction disturbance).	tricyclic anti-depressants	Above plus treatment for atrial arrhythmias conduction disurbances. i.v. $NaHCO_3$ to maintain arterial pH above 7.45
	as above	antihistamines	Supportive
	as above; extrapyramidal symptoms	phenothiazines	Supportive; diphenhydramine 2–3 mg/kg i.v. for extrapyramidal symptoms
3. Rapid onset shock & gastroenteritis and dyspnea	non-responsive hypotension, vomiting, tachypnea, pulmonary edema, dyspnea, altered sensorium, atrial/ ventricular arrhythmias	aluminium phosphide	No specific antidote i.v. $NaHCO_3$ to correct acidosis
4. Sympathomimetic	tachycardia, hypertension, seizures, arrhythmias, excitation, tremors	amphetamines	Forced acid diuresis β-blockers for arrhythmias
	as above	cocaine β agonists aminophylline	Supportive β-blockers Discontinue agent
5. Cyanosis	cyanosis, smell of bitter almonds, dyspnea, coma, atrial fibrillation	hydrogen cyanide	1. Amyl nitrite (1 pearl under the nostril X 1 minute) 2. 3% sodium nitrite 300 mg i.v. over 5 minutes (10 ml) 3. Sodium thiosulfate (25%) 50 ml (ie) 12.5 g i.v. over 10 minutes

the offending current. The respiratory support measures are immediately initiated and the patient defibrillated if indicated. Once resuscitative measures are successful, a careful examination is necessary to rule out associated musculoskeletal injury as well as to initiate careful monitoring for evidence of myoglobinuria.

Near-drowning

Pathophysiology Drowning refers to the submersion of a subject in a liquid medium, usually fresh or salt water. Attempts have been made in literature to distinguish *fresh water drowning*, with its accompanying hypervolemia, hemodilution and hemolysis, from *salt water drowning* with its accompanying hypovolemia and hypernatremia. Such differences are largely theoretical and rarely encountered practically. In reality, the pathophysiology of fresh- or salt-water drowning is similar and related to aspiration-induced pulmonary injury and hypoxic central nervous system insult.

Aspiration of water results in flooded alveoli and loss of alveolar surfactant. This promotes atelectasis and intrapulmonary shunting. The net result is hypoxemia that has a respiratory basis, and acidosis that has a metabolic basis (due to tissue hypoxia). Hypothermia is an additional hazard due to cold-water immersion. Anoxic encephalopathy may result and lead to cerebral edema. Arrhythmias and hypotension may also be found due to tissue hypoxemia. Uncommon complications that may be encountered include intravascular hemolysis and a state of disseminated intravascular coagulation.

Management The keystone of treatment is the relief of hypoxia with respiratory support and reversal of acidosis with sodium bicarbonate (titrated according to arterial blood gas analysis). Isotonic saline or Ringer's lactate is administered to restore intravascular volume. A Ryle's tube is inserted to empty the stomach of swallowed water. Cerebral edema is treated with osmotic diuretics and hyperventilation (to maintain a PCO_2 of 25–30 mmHg).

Hypothermia

Hypothermia is defined as a core temperature of 35.5°C (96°F) or less. Clinical thermometers are often calibrated only as low as 35°C. Hence the clinical severity of hypothermia may be underestimated. The causes of hypothermia are listed in Table 18.2.

Pathophysiology The normal physiologic response to exposure to cold comprises cutaneous vasoconstriction (to reduce heat loss), tachycardia (due to catecholamine release), shivering (to produce heat, that is, *shivering thermogenesis*) and diuresis. As the core temperature falls below 32°C (90°F), muscular rigidity replaces shivering and the sensorium becomes 'beclouded'. There is a fall in blood pressure, and the ECG changes include sinus

Table 18.2 Causes and predisposing factors of hypothermia

1. Endocrine causes
   - myxedema
   - hypopituitarism
   - adrenal insufficiency
   - hypoglycemia
   - diabetic ketoacidosis
2. Drug intoxication
   - sedatives
   - ethanol
   - opiates
   - phenothiazines
3. CNS lesions
   - hypothalamic lesions
   - Wernicke's encephalopathy
   - cerebrovascular accidents
4. Bacterial sepsis
5. Iatrogenic hypothermia
   - cold blood transfusion
   - antipyretics
6. Accidental exposure to cold

bradycardia, prolongation of all electrocardiographic intervals (P-R, QRS, Q-T intervals) and the development of *J waves* (abnormal terminal deflection of the QRS complex). Gastrointestinal motility is reduced and ileus is common. Below 30°C (85°F), atrial fibrillation ensues and there is loss of voluntary motion. Renal glomerular and tubular functions both decrease in tandem so that urine production is maintained upto 27°C (81°F). Below this, ventricular fibrillation occurs spontaneously and renal shutdown ensues.

The metabolic correlates of hypothermia include acidosis (due to decrease in tissue oxygen delivery, shift to left of the oxyhemoglobin dissociation curve), hyponatremia and hyperkalemia (due to cold-induced inhibition of the Na^+–K^+ ATPase pump) and hemoconcentration.

Management Treatment is aimed at resuscitation of the patient and rewarming. Cardiopulmonary resuscitation is unlikely to succeed if the core temperature is less than 28°C and efforts at resuscitation must be continued until the core temperature exceeds 32°C. The method for rewarming and the rate of rewarming are dictated by the specific clinical situation. If endogenous heat production mechanisms such as shivering are functioning, *passive rewarming* can be attempted by protecting from further heat loss. On the other hand, in the elderly, in the case of immersion victims, or when the endogenous heat production mechanisms are defunct, the patient is rewarmed actively. This may be accomplished by *active external rewarming* (such as a warm bath at 40–45°C) or by *core rewarming* (by extracorporeal circulation, peritoneal dialysis with warmed potassium-free dialysate or by inhalation of warm gases). Often non-invasive methods are preferred to invasive methods as both have comparable efficacy.

It must be kept in mind that during rewarming, any manipulation (such as tracheal intubation) is to be kept to the minimum due to the risk of ventricular fibrillation. Once the temperature rises to over 30°C, this risk diminishes.

Heat-related Disorders

Pathophysiology and etiology Normal core temperature is maintained within a narrow range by hypothalamic heat regulatory centres. Dissipation of body heat occurs by radiation, convection and conduction from the integument, by evaporation from the integument and by warming of inspired air. When the ambient temperature approaches 35°C (95°F), gradient-dependent heat-loss measures, like radiation and convection, become inefficient and evaporation becomes the major mode of heat loss. Heat toxicity supervenes when these body defence measures are overworked or rendered inefficient.

The etiologic causes and predisposing factors are listed in Table 18.3.

Table 18.3 Factors predisposing to heat stroke

1. Environment-related
   - elevated ambient temperature, relative humidity
   - obesity
   - old age
   - strenuous exercise
   - fever
   - dehydration
2. Central Nervous System disease
   - hypothalamic disease
   - autonomic neuropathy
   - delirium tremens
3. Skin disease
   - scleroderma
   - congenital anhidrosis
4. Drug intake
   - phenothiazines (neuroleptic malignant syndrome)
   - anticholinergic
   - antihistamine therapy
   - amphetamine abuse
5. Anesthesia-related
   - malignant hyperthermia

Clinical features *Heat cramps* are the mildest and most common form of illness, occurring in the frequently-used muscles. The complaints of cramps usually occur during exercise and are related to salt depletion through perspiration, especially when replacements have been through inappropriate hypotonic solutions.

Heat exhaustion is a syndrome of exhaustion, headache, nausea, thirst, malaise and muscle cramps occurring over several days due to the combined loss of salt and fluids. Hyperpyrexia generally does not occur.

Heat stroke, on the other hand, is characterised by hyperpyrexia, with the core temperature usually exceeding 41°C (106°F).

Two categories of heat stroke are recognised. The *classical heat stroke* develops gradually over days, in older individuals, after prolonged exposure to unusually hot weather. The victims are often overclothed or have deficient thirst mechanisms. They are dehydrated and anhidrotic. *Exertional heat stroke* occurs in younger, unacclimatised individuals, developing over a period of hours after strenuous exercise in a warm and humid environment. Perspiration is still detectable and the initial symptoms may be of extreme weakness or confusion. This syndrome entails a higher risk of renal failure (25 per cent) as compared to subjects with a classical heat stroke.

Common features of either forms of heat stroke include hyperpyrexia, hyperventilation with consequent respiratory alkalosis, altered sensorium and/or coma, hypotension (due to myocardial depression as well as hypovolemia) and occasionally, seizures. Laboratory tests reveal hypokalemia, hypocalcemia, hypophosphatemia and elevated serum transaminases and CPK (reflecting liver and muscle injury). Coagulation studies may reveal evidence of intravascular coagulation.

The '*neuroleptic malignant syndrome*' is an infrequent though potentially lethal complication of antipsychotic drugs. The drugs,

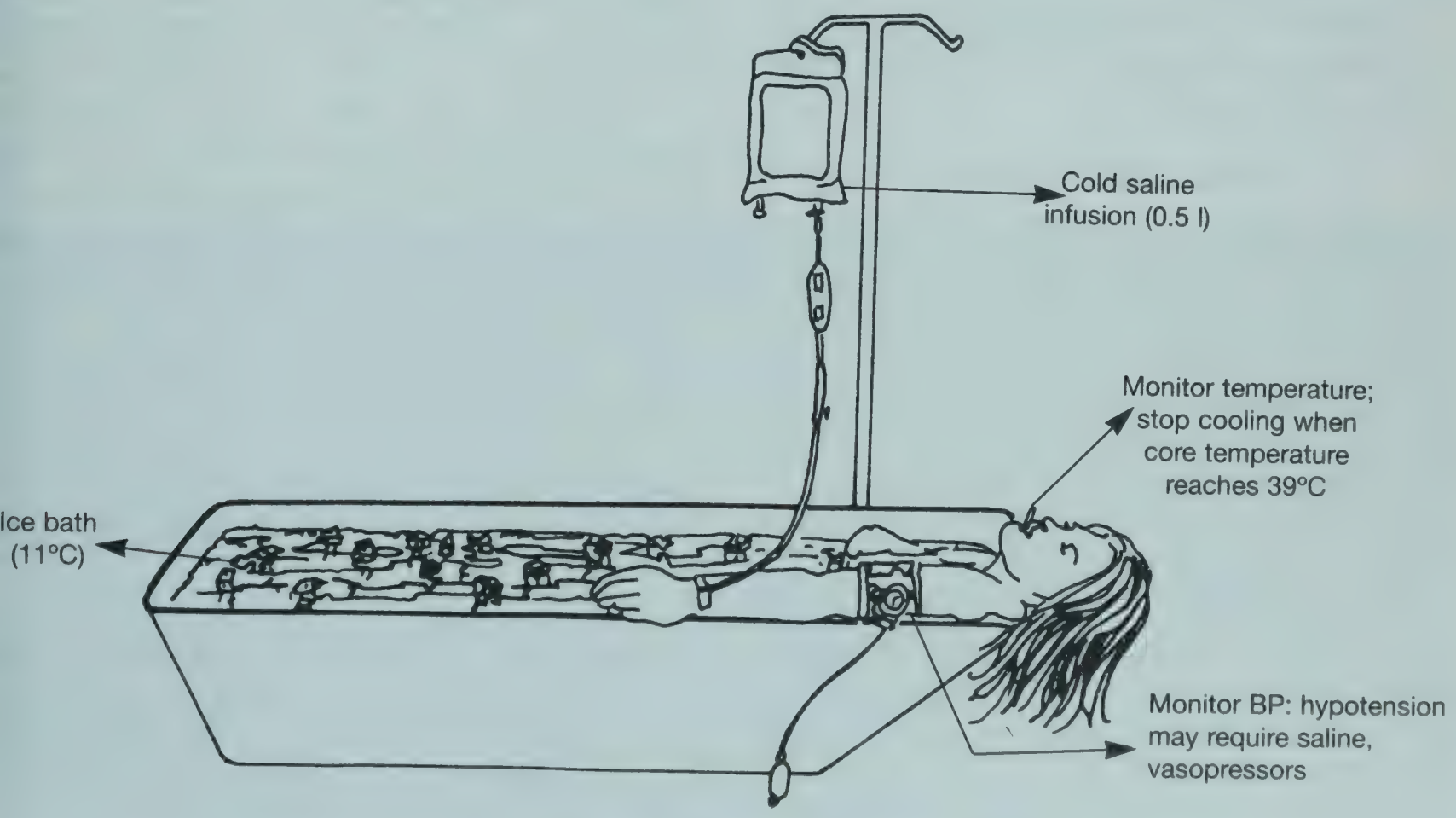


Fig 18.1 Management therapy for heat stroke

especially phenothiazines, block the dopaminergic regulation of muscular tone and autonomic function. The syndrome is characterised by hyperpyrexia, extrapyramidal symptoms and neurologic signs, that is, generalised rigidity, akinesia, altered sensorium and autonomic disturbances. It can lead to rhabdomyolysis, myoglobinuria and acute renal failure.

Management (Fig 18.1) The aim of therapy in heat stroke is to rapidly lower the core temperature to below 39°C in 30–60 minutes, correct volume deficits and remove the victim from the inciting influence. Rapid cooling can be achieved by tepid sponging with water and directing a fan over the victim. The use of aspirin, chlorpromazine or alpha adrenergic vasoconstrictors is usually not recommended and steroids are of little benefit. Neuroleptic malignant syndrome responds to bromocriptine and dantrolene, agents which restore central dopaminergic mechanisms and relax muscle tone, respectively.

Treatment of heat cramps or heat exhaustion is by proper salt repletion and salt and volume replacement, respectively.

High Altitude Diseases

Pathophysiology At high altitudes, the partial pressure of oxygen in inspired air declines commensurate with the low barometric pressure. At an altitude of 10,000 feet (3050 metres) the partial pressure of oxygen is 60 mmHg and this falls on the steep downslope of the oxyhemoglobin dissociation curve. Any further drop in PO_2 is associated with a steep fall in arterial oxygen saturation.

Acute mountain sickness (AMS) is a self-limited illness characterised by headache, anorexia, malaise and is due to the rapid ascent of an unacclimatised person to an altitude of more than 8000–10,000 feet.

High altitude pulmonary edema (HAPE) is a potentially fatal form of 'non-cardiogenic' pulmonary edema occurring due to the increased pressure and permeability of pulmonary capillaries. It usually occurs 8–40 hours after rapid ascent to a high altitude.

High altitude cerebral edema (HACE) is characterised by progressive headache, confusion, ataxia and hallucinations presumably related to hypoxic cerebral edema. Cerebral vasodilatation due to hypoxemia may be contributory. At altitudes above 14,000 feet, peripheral dot hemorrhages may appear in the retina (high altitude retinal hemorrhage).

The term *chronic mountain sickness* refers to cor pulmonale in long term residents of high altitude due to chronic hypoxia.

The definitive treatment of high altitude related diseases is administration of oxygen and rapid descent to a lower altitude.

Radiation Injury

Pathophysiology Injury from radiation exposure may be due to thermal injury or due to ionising radiations. Acute whole body radiation occurs as a consequence of nuclear reactor accidents or malfunction of accelerator. With doses less than 3 Gy (1 Gy = 1 joule/kg), nausea and vomiting are seen. The *hematologic syndrome* occurs at exposure doses of 10–12 Gy and consists of purpura, leukopenia and fever. Recovery is common if the dose of exposure is in this range. The *gastrointestinal syndrome* occurs at doses of 12–30 Gy and is usually fatal. Small bowel diarrhea, and life-threatening infectious enteritis occurs in this syndrome. The *cardiovascular-central nervous system syndrome* occurs at doses of 30–50 Gy and is invariably fatal. Ataxia and shock are the main features.

Management The essence of therapy lies in precautions to prevent nuclear accidents. Bone marrow transplantation has been used for the hematologic syndrome after exposure to 7–10 Gy, provided a good donor match is found.

Snake Bite

Epidemiology Snake bites may occur either on land or in water. Most land and aquatic snakes are non-poisonous. Most bites of poisonous snakes also do not result in *envenomation* (the presence of venom in the victim's blood). Men are victims more often than women and the majority of bites are incurred in tropical jungles where people walk barefoot and are scantily clothed. Snakes generally bite only on being provoked or disturbed; it is a defence mechanism as a reaction to a perceived threat.

Pathophysiology After a snake bite, the locally injected venom (of the poisonous snake) is transported systemically by the lymphatics of the skin and the subcutaneous tissue. Absorption of venom is rapid if it is injected into a vessel by chance, if the lymphatic flow of the limb is increased by vigorous movement of the limb or if there is injection 'into' the eye (spitting cobra). The local reaction depends on the type of venom as does the systemic reaction (Table 18.4).

Management First aid is given to the victim by first reassuring him and by immobilising the limb with a splint. A crepe bandage or a tourniquet (tight enough to decrease lymphatic flow but not obliterating the arterial pulse distally) is applied proximally. The victim is transported to the hospital where he is admitted for observation for 12–24 hours. Incision of the puncture site and suction are not recommended. The victim is monitored for evidence of local or systemic envenomation; the two may occur together, and even in the absence of envenomation urine output and blood clotting tests are monitored. If there is no evidence of envenomation at 12–24 hours, the victim may be discharged. Specific antivenin is indicated if there is any evidence of systemic envenomation (irrespective of time after the bite), or if there is evidence of local necrosis and the victim is seen within six hours of the bite. Only a small minority of patients need the antivenom. Polyvalent antivenin may be used if systemic effects do not clearly identify the culprit snake species. The tourniquet is released only in hospital as serum venom levels may rise dramatically thereafter.

Table 18.4 Comparison of the toxicity of common venomous snakes

	Viper venom	*Cobra/Krait venom*	*Sea snake venom*
Main toxicity	Vasculotoxic	Neurotoxic	Myotoxic
Envenomation	Very common	Common	Occasionally
Local symptoms (swelling, necrosis)	+++ Russell's viper bite	++	None
Systemic symptoms	Bleeding from gums, skin, urine, sputum (DIC)	Ptosis, respiratory paresis, dysphagia, dysphonia, nasal regurgitation	Myalgia, myoglobinuria
Dose of specific antivenin*	2–10 ampoules	10–50 ampoules	2–10 ampoules

* administered after skin test to exclude hypersensitivity to equine serum; 1 ampoule = 10 ml

KEY CONCEPTS

Poisoning

- Poisoning may be suicidal, accidental or homicidal in intent. Common poisonings in our country include the ingestion of organophosphates, datura, copper sulphate, aluminium phosphide, methanol and kerosene.
- When evaluating a patient with suspected poisoning, the first step is to assess the patency of airways and the adequacy of respiratory effort and circulation. Steps for resuscitation should accordingly be initiated. While resuscitation is proceeding, a history may be obtained from the attendant about the nature of the ingested substance.
- General measures include a gastric lavage if the gag reflex is intact, the poison is not a corrosive (or a petroleum distillate) and was ingested less than 4 hours earlier. A sample of the gastric contents should be preserved for toxicologic investigation. Forced alkaline diuresis is useful for barbiturate and aspirin poisonings. Hemodialysis may have a role if the ingested substance is dialysable.
- Physical examination should be targeted toward identifying any combination of signs which may suggest the nature of the poison. If there is increased sweating, salivation, bradycardia, rhinorrhea, miosis and slurring of speech, a cholinergic syndrome is present and the etiology could be organophosphate poisoning; treatment with atropine and pralidoxime can be initiated. If there is a dry flushed appearance, tachycardia, urinary retention, dilated pupils, and hyperpyrexia, an anticholinergic syndrome is present. This could be due to datura poisoning or tricyclic antidepressant overdose. Treatment is with physostigmine. Methanol poisoning should be suspected in any patient who complains of blindness, dizziness, headaches and exhibits incoordination (suggestive of alcohol intoxication); intravenous ethanol and correction of acidosis are recommended. Presence of an extrapyramidal syndrome with torticollis suggests phenothiazine intake; diphenhydramine usually provides relief.

Electrical injury

- Electrical injury varies depending on the nature of the current, its voltage and ampeerage, the resistance of the host and the duration of contact.
- AC current is more dangerous than DC current. The extent of damage varies directly with the voltage, the ampeerage and the duration of contact. If the skin is moist or if the contact point is the upper extremity, the hazard is greater. Electrical injury results in involuntary muscular contractions, seizures and ventricular fibrillation (and cardiac arrest).
- Effective grounding of electrical devices and ground-fault circuit breakers are important preventive measures.

Drowning

- Injury occurs in the drowning victim due to two mechanisms: immersion (cold exposure) and aspiration.
- Reflex laryngospasm can result in asphyxiation (dry drowning). Fresh and salt water cause a similar extent of pulmonary injury. Hypoxemia results in metabolic acidosis, respiratory depression, cyanosis, cerebral anoxia and coma. Cardiac effects include ventricular fibrillation and hypotension.
- The clinical setting is suggestive and a chest X-ray should be obtained to assess the extent of aspiration injury (pulmonary infiltrates). The ECG may show J waves if hypothermia is present.
- Treatment measures include ensuring adequate ventilation, intravenous fluids, and antibiotics for infection. If hypothermia is present, passive rewarming is initiated. Raised intracranial pressure, if present, must be lowered.

Heat exposure

- Exposure to a high ambient temperature can result in heat cramps, heat exhaustion, or heat stroke (heat hyperpyrexia).
- Heat cramps result from excessive loss of sodium in the sweat. The vital signs are preserved and the involved muscle may feel like a tight knot. Treatment consists of encouraging oral drinks containing salt.
- Heat exhaustion results from excessive sweating and loss of fluids with consequent hypovolemia. The patient appears fatigued and drenched with sweat. The skin is cold and clammy, the blood pressure is low and the core temperature is normal. Treatment consists of oral cool salty drinks and, if required, intravenous saline.
- Heat stroke results from a failure of the normal sweating mechanisms for lowering body temperature. The skin appears hot and flushed. There is tachycardia, hypotension and the core temperature is more than 40° C. Treatment consists of wrapping the patient in a wet bedding or placing her in a tub of cold water. Supportive measures include administration of intravenous fluids and maintenance of electrolyte balance. It is important to monitor core temperature to obviate hypothermia due to an excessive lowering of core temperature.

High altitude disease

➢ A rapid ascent to a height of 2500 metres or higher can result in acute mountain sickness. Clinical manifestations include headache, nausea, vomiting, and fluid retention. High altitude pulmonary edema manifests as worsening dyspnea, tachycardia and cyanosis. High altitude cerebral edema results in headaches, ataxia and confusion.

➢ Chronic mountain sickness results in polycythemia, cyanosis, pulmonary hypertension and cor pulmonale.

➢ A diagnosis of high altitude-related disease is readily made from the clinical setting.

➢ Treatment of acute mountain sickness includes oxygen administration, dexmethasone (for cerebral edema), diuretics (for pulmonary edema) and rapid descent to a lower altitude. Prophylactic administration of acetazolamide and provision for acclimatisation are important preventive measures.

➢ Chronic mountain sickness is treated with domiciliary nocturnal oxygen administration, phlebotomy (for polycythemia) and the use of respiratory stimulants (medroxyprogesterone or acetazolamide).

Radiation injury

➢ 1 Gray (Gy) = 100 rads. Tissues with an increased cell turnover are more susceptible to radiation; in order of decreasing susceptibility, these include the lymphocytes, gonads, bone marrow, bowel epithelium, skin, hepatocytes, nerve cells, muscle and connective tissue.

➢ Acute exposure to radiation can result in three syndromes depending on the dose of exposure. At exposure levels of 2–10 Gy, a hematopoietic syndrome results and is characterised by nausea, vomiting, pancytopenia and an increased susceptibility to infection. Exposure levels of >4 Gy result in the gastrointestinal syndrome; nausea, vomiting, diarrhea, dehydration and vascular collapse result. When the exposure level is >30 Gy, the cerebral syndrome occurs and is invariably fatal. It is characterised by diffuse cerebral dysfunction.

➢ Delayed effects of radiation exposure include cataract, reduced fertility and the increased risk of certain cancers (thyroid, leukemia, skin and bone).

➢ Treatment of acute radiation injury is supportive.

Snake bite

➢ Clinical manifestations depend on the presence or absence of envenomation and the specific venom injected. Viperine venom causes endothelial damage and coagulation defects. Elapid (cobra) venom interferes with neuromuscular transmission.

➢ Bite by a viper results in local edema, swelling, pain and the progressive evidence of hemorrhage (ecchymoses). Local signs may be minimal in a cobra bite; paresthesiae around the bite, visual disturbances (diplopia), difficulty in phonation, swallowing and muscular incoordination may be present.

➢ The patient must be reassured and transported to a centre equipped to treat such cases. Important investigations include a blood count, coagulation profile, renal functions and a 12-lead ECG.

➢ Antivenin (3–15 ampoules) must be administered immediately (after a skin test to exclude hypersensitivity to equine serum). Supportive measures include administration of intravenous fluids, fresh frozen plasma (if there is a coagulopathy), and respiratory support (if required).

19

Occupational Health

The WHO has defined occupational health thus: Occupational health should aim at the promotion and maintenance of the highest degree of physical, mental and social wellbeing of workers in all occupations, the prevention of ill health among workers which is caused by their working conditions, the protection of workers in their employment from risks resulting from factors adverse to health; the placing and maintenance of the worker in an occupational environment adapted to her physiological and psychological equipment and, to summarise, the adaptation of work to person and, of each person to the job.

In occupational medicine there are four basic categories of hazards: physical, biological, chemical and psychological. Table 19.1 summarises some of these hazards and the resultant occupational diseases.

Occupational–Environmental history

This relevant information is always to be sought in every patient. An enquiry is made to ascertain if symptoms are specifically associated with work days, and relief over weekends. A history of exposure to dust, fumes or chemicals in daily activities or during recreational activities (painting, sculpture, woodwork, archeology) is actively sought. Although occupational diseases are a large category in themselves, a discussion of occupational pulmonary diseases is provided in this chapter.

Occupational asthma

Occupational asthma is defined as asthma occurring in a previously healthy individual as a result of occupational exposure.

Etiology and pathophysiology Occupational asthma may arise either due to acute non-immune airway injury and inflammation, or due to immediate hypersensitivity to altered tissue proteins. Provoking agents include isocyanates (plastics, varnishes), anhydrides (epoxy resins), wood dust (saw mills), plant dust (agricultural workers) and metal salts (metal plating, tanning).

Diagnosis A history of wheezing and dyspnea at the work site especially towards the evenings with relief obtained at home is highly suggestive of occupational asthma. A change in PEFR (peak expiratory flow rate) of more than 20 per cent from home to the work site (with deterioration at the work site) is diagnostic of the disorder.

Treatment The mainstay of treatment is the avoidance of exposure to the inciting agent if it can be identified. Acute attacks may require bronchodilator drugs such as aerosols or nebulisers, along with removal of the subject from the place of work.

Silicosis

Silicosis refers to parenchymal lung disease caused by inhalation of particles of silicon

Table 19.1 Occupational diseases

Agent	*Occupation leading to exposure*	*Hazards*
Chemical agents		
1. Dusts (pneumoconiosis)		
a. Inorganic dusts		
Coal dust	Coal mining	Anthracosis
Silica	Mica, ceramics industry, sand blasting	Silicosis
Asbestos	Cement, fire-proofing, textiles	Asbestosis
b. Organic dusts		
Cotton dust	Textile industry	Byssinosis
Cane fibre	Sugarcane, paper, cardboard industries	Bagassosis
Hay	Agricultural work	Farmer's lung
2. Metals		
Beryllium	Mining of beryllium	Berylliosis
Maganese	Mining	Parkinsonism
Lead	Automobile industry	Plumbism
3. Gases		
Carbon monoxide, Chlorine, phosgene	Coal gas, plants, steel industry	Asphyxiation Adult respiratory distress syndrome
Physical agents		
1. Heat	Jute, mining	Hyperpyrexia
2. Cold	Cold work	Frost bite, chillblains
3. Light	Mining	Miner's nystagmus, cataract
4. Noise	Factories (all)	Deafness
5. Radiation	Welding, radiopharmaceutical industry	Cancer, aplastic anemia
6. Electricity	Factories (all)	Burns
7. Vibration	Pneumatic tools	Raynaud's phenomenon
Occupational cancers		
Skin	Gas workers, road makers, dye makers	Squamous cell carcinoma
Lungs	Mining, radioactive substances	Lung carcinoma
Bladder	Rubber, dye stuff, electric cable industries	Bladder cancer
Psychological		
Stress	All types	Neurosis
Work-shift changes	of occupation	Hypertension
Biological agents		
Animals	Agriculture, live stock breeding	Zoonotic infections

dioxide. Working in industries which are involved in quarrying, stone cutting, tunnelling, and mining can result in exposure to high concentrations of silica. *Acute silicosis* is due to massive exposure to silica usually within five years of start of exposure. *Chronic silicosis* has an onset typically 15 years after exposure and *accelerated silicosis* has an onset of symptomatology 5–15 years after exposure.

Pathology and pathogenesis Silica crystals lodged in the alveoli provoke a response by alveolar macrophages. In acute silicosis there is an outpouring of an eosinophilic exudate into the alveolar space. In chronic silicosis, the crystals lie in the phagolysosomes of the macrophages and provoke an intense fibrogenic response. Nodules with a central acellular core of collagen and a cellular peripheral capsule

(macrophages, plasma cells and fibroblasts) result and these can coalesce to form large masses (*progressive massive fibrosis*). The nodules have a characteristic whorled appearance, and the appearance of scattered birefringent silica crystals on examination by polarised light is diagnostic.

Epidemiology Silicosis was first reported in India from the Kolar gold mines (Karnataka). The prevalence varies from 15 per cent (in ceramic industry) to 30 per cent (in mica mines). Silica particles between 0.5 μ and 3 μ in size are the most hazardous.

Clinical features Chronic silicosis usually presents as asymptomatic roentgenologic abnormalities. When symptoms do occur, dyspnea of a mild degree is the commonest manifestation. Severe dyspnea often indicates underlying 'progressive massive fibrosis'. There is an increased susceptibility to mycobacterial infections (typical and atypical mycobacterioses) and fungal disease.

The chest X-ray shows multiple small nodules preferentially in the upper lobe (*simple silicosis*), with or without hilar adenopathy with a typical *egg shell calcification.*[1] In patients with progressive massive fibrosis (*complicated silicosis*) conglomerate large shadows may be seen, especially symmetrical and in the perihilar region (*batwing configuration*). Pulmonary function tests reveal a mixed 'obstructive-cum restrictive' defect and are useful for quantifying the extent of pulmonary impairment.

Treatment and prevention There is no definitive treatment for silicosis.

Preventive measures are of utmost importance and include rigorous dust control measures, substitution of alternatives to silica, use of respiratory protective devices by workers and regular physical examination of workers.

[1] Egg shell calcification – outer rim of calcification

Anthracosis or Coal Worker's Pneumoconiosis (CWP)

Anthracosis is a parenchymal lung disease caused by the inhalation of coal dust.

Epidemiology Anthracosis occurs mainly in coal miners but can also occur in graphite miners, and on exposure to carbon black (electrode manufacture). The average risk of death among coal miners is nearly twice that of the general population. Part of this excess risk may be due to anthracosis.

Pathology and pathogenesis The typical pathologic lesion is the '*coal macule*' which contains a large number of alveolar macrophages with their ingested 'dust'. Collagen is scarce in the macules. On occasion, as in silicosis, the macules, can coalesce into 'conglomerate masses' resulting in progressive massive fibrosis (PMF). They are predominant in the posterior segment of the upper lobes, the superior segment of the upper lobes and the superior segment of the lower lobes.

The exact pathogenesis of PMF is not clear as coal dust itself is not fibrogenic. Perhaps a concomitant infection or an immunologic abnormality triggers off release of monokines that stimulate fibroblasts to produce collagen.

The association of coal worker's pneumoconiosis, rheumatoid arthritis and conglomerate pulmonary nodules is referred to as the *Caplan syndrome.*

Clinical features Like silicosis, anthracosis most often presents with the asymptomatic presence of small irregular opacities in the chest X-ray. There may be associated chronic bronchitis and obstructive airway disease (due to coal dust-related mucous hypersecretion). Dyspnea of a moderate or severe degree usually reflects complicated pneumoconiosis, that is, progressive massive fibrosis.

Pulmonary function tests reveal a combined 'restrictive-cum-obstructive' ventilatory

impairment and are useful for prognostication and follow-up.

Treatment There is no definitive treatment other than supportive care. Preventive measures are, therefore, essential and include dust control measures, the periodic health surveillance of workers and the use of protective masks.

Asbestosis and Asbestos-related Diseases

Asbestosis refers to non-malignant pulmonary disease, related etiologically to asbestos exposure. *Asbestos-related diseases* include a broader range of clinical disorders related to inhaled asbestos such as pleural fibrosis and effusion, pleuroperitoneal mesotheliomas, cancer of lung, larynx and gastrointestinal tract.

Pathophysiology Asbestos fibres are of four types which belong to one of two categories: the *serpentine* fibres are curved and comprise the *crocidolite* fibres whereas the *amphibole* fibres are straight and are one of three types—*chrysotile* (blue), *amosite* and *anthophyllite*. The amphibole fibres are more fibrogenic and carcinogenic. Exposure to asbestos occurs in the cement industry and in factories involved in the manufacture of brakes and insulation.

The inhaled asbestos fibres are coated in the lung alveoli to form *asbestos bodies*. These asbestos bodies may be seen in the sputum also. They, however, reflect only prior asbestos exposure and are not diagnostic of asbestosis. In the alveoli, the asbestos bodies initially incite a peribronchiolar inflammation followed by an interstitial fibrogenic response. There may be an acellular collagenous response in the parietal pleura with a tendency to calcify—this is called the *pleural plaque*. These plaques are often bilateral and are distributed over the diaphragmatic pleura. The pulmonary reaction is more often at the lung bases. Malignant transformation within the pulmonary parenchyma may also occur; this is dependent on the duration of exposure and the cumulative dose of asbestos inhaled. Asbestos-related pulmonary disease requires several years of exposure, often more than 15 years.

Clinical features The pathophysiologic hallmark of asbestos-related interstitial fibrosis is a 'restrictive' ventilatory defect which is clinically manifested as exertional dyspnea. Pleural disease is detected usually on a routine chest X-ray as bilateral calcified plaques which are asymptomatic. Pleural effusion may either occur in association with plaques, or may be due to a malignant pleural mesothelioma.

Asbestos exposure is also associated with increased risk of cancer of the larynx, the lung and the gastrointestinal tract.

Treatment There is no definitive treatment of asbestosis. Measures for the prevention of exposure and limiting the dose of exposure are similar as for other pneumoconioses.

KEY CONCEPTS

Occupational lung disease

- The common occupational lung diseases include occupational asthma, coal worker's pneumoconioses, silicosis and asbestosis.
- Inhaled fibrogenic dust lodges in the alveoli and provokes a fibrogenic response from the alveolar macrophages.
- There is no specific treatment other than removal from the source of exposure, the use of protective devices by workers at such facilities and the periodic surveillance of the healthy workers.

Occupational asthma

- Occupational exposure typically results from exposure to inorganic compounds (isocyanates, Ni, Cr) and organic agents (enzymes) which are allergenic and result in heightened bronchial reactivity.

- ➢ Typically, there is wheezing which increases in the evenings after the working hours and which is relieved over the weekends only to reappear again with resumption of work.
- ➢ Treatment consists of removal from the source of exposure or the use of masks or protective devices (in case removal is not possible). Disodium cromoglycate may be used for prophylaxis.

Silicosis

- ➢ Silicosis is an occupational disease which occurs when there is prolonged (20 years) exposure to crystalline quartz (mining, stone cutting industries).
- ➢ Chronic silicosis results in upper zone pulmonary fibrosis and egg shell calcification of the hilar lymph nodes.
- ➢ Chronic silicosis presents with dyspnea, cough and restrictive lung disease. An acute variant occurs after a shorter duration of exposure and is associated with a very high mortality. Progressive massive fibrosis results in the formation of conglomerate pulmonary masses.
- ➢ There is no specific treatment other than removal from the source of exposure.

Asbestosis

- ➢ The severity of pulmonary asbestosis depends on the duration and severity of exposure.
- ➢ Asbestosis results in a restrictive lung physiology. Progressive dyspnea and cough are the principal symptoms. The classical radiologic findings include calcified pleural plaques and a ground glass appearance of the lower lung fields.
- ➢ There is an increased risk of pleuroperitoneal mesothelioma. There is also an increased risk of bronchogenic carcinoma (which is multiplied several fold in smokers).

20

Pregnancy-related Medicine

ASTHMA IN PREGNANCY

Asthma has been reported to occur in upto one per cent of pregnant women, making it the most common form of obstructive airway disease in pregnancy. To understand the complexities in the interaction of an asthmatic state with pregnancy, the normal changes in the respiratory system with pregnancy must be recapitulated. Pregnancy is associated with an increase in tidal volume, though the respiratory frequency and vital capacity are unchanged. The result is an increase in minute ventilation probably induced by the respiratory stimulant activity of progesterone. There is a small decrease in total lung capacity but no change in airway resistance. Arterial blood gases reveal a compensated respiratory alkalosis due to hyperventilation.

Effect of asthma on pregnancy

Uncontrolled asthma can result in prematurity, low birthweight, and increased perinatal and maternal mortality. However, the outcome in controlled asthma during pregnancy is as favourable as that for pregnancy in the general population.

While theophyllines, epinephrine, disodium cromoglycate and corticosteroids are safe in pregnancy, some concern has been voiced about the use of beta agonists. These agents relax the uterus, and the safety of the newer agents in pregnancy has not been adequately established.

Effect of pregnancy on asthma

There is no consistent effect of pregnancy on the course of asthma, with reports of increased and decreased severity of disease being noted.

INFLAMMATORY BOWEL DISEASE IN PREGNANCY

Effect of inflammatory bowel disease on pregnancy

In general, most surveys indicate that women with chronic inflammatory bowel disease have about the same overall chance of giving birth to a normal healthy infant as do healthy women, especially if the disease is quiescent. In pregnant subjects with severe colitis, however, the chances of abortion are higher as compared to the general population.

Effect of pregnancy on inflammatory bowel disease

Patients with inflammatory bowel disease have a milder course during pregnancy particularly if their disease is quiescent at the time of conception. Pregnancy does not increase the likelihood of an acute attack. When attacks of colitis do occur, they are more likely during the first trimester and in the postpartum period. Diagnostic procedures are generally avoided unless they are likely to substantially affect disease management. Though corticosteroids are safe in pregnancy, sulphasalazine is best avoided in the asymptomatic pregnant patient because it crosses the placenta and can displace

bilirubin from albumin, increasing the likelihood of kernicterus in the fetus.

HEPATITIS IN PREGNANCY

The commonest type of hepatitis in pregnancy is viral hepatitis. The most frequently encountered form of viral hepatitis is infection with hepatitis A virus. Other causes of jaundice in pregnancy include acute fatty liver of pregnancy, benign recurrent intrahepatic cholestasis (BRIC), drug-induced hepatitis and preeclampsia.

Effect of viral hepatitis on pregnancy

Most pregnant patients with viral hepatitis have an uneventful course if cared for properly, unless they have underlying nutritional problems. The main risk is one of maternofetal transmission of the hepatitis virus. Hepatitis A virus is not transmitted from the mother to the offspring. Women who have hepatitis B infection in the first or second trimester also hardly ever transmit the infection to their neonates. However, such a transmission is likely in hepatitis B occurring in the third trimester (60 per cent)[1] and in chronic carriers of hepatitis B. Most cases of infected infants are due to exposure at the time of delivery. The high rate of HBsAg carriers in the southeast Asian population is assumed to have evolved through sequential maternal-offspring transmission. Mothers with antibody to hepatitis B 'e' antigen are unlikely to transmit the virus, whereas mothers with serologic presence of the hepatitis B 'e' antigen (an indirect indication of viral replication) are highly likely to transmit the infection to the offspring.

Prevention of neonatal hepatitis B can be achieved by administering hepatitis B immunoglobulin (0.5 ml i.m.) followed by hepatitis B vaccine (0.5 ml [10mg]), both within 12 hours of birth, with additional doses of the vaccine at one and six months.

1 The placental 'barrier' gradually decreases in efficacy as the pregancy advances.

Effect of pregnancy on viral hepatitis

Current evidence suggests that pregnancy does not affect the clinical course of viral hepatitis.

Acute Fatty Liver in Pregnancy

This is an uncommon but potentially fatal disorder usually occurring towards the end of the third trimester of pregnancy, most often in the thirtyfifth week. If untreated it can progress to fulminant hepatic failure with its attendant complications of encephalopathy and coagulopathy. Early diagnosis, rapid termination of pregnancy and intensive supportive treatment have led to a sharp decline in fetal and maternal mortality rates from 85 per cent in the past to 20 per cent currently.

CARDIOVASCULAR DISORDERS IN PREGNANCY

To understand the effect of congenital and acquired heart disease on the pregnant state and vice versa, an understanding of the hemodynamic changes in normal pregnancy is essential. The pregnant state is characterised by a fall in peripheral vascular resistance, pulmonary resistance and systemic blood pressure; there is an increase in the blood volume, cardiac output, stroke volume and heart rate. The fall in vascular resistance occurs early in pregnancy, probably under the influence of estrogenic hormones, and is maintained throughout pregnancy, probably under the influence of increased levels of prostacyclins later. The blood volume increases by 40 per cent (a 50 per cent increase in plasma volume and a 30 per cent increase in erythrocyte mass) by the 30th week. The cardiac output is also increased by 40 per cent but this level is achieved by the twentieth week of gestation.

Effect of cardiac disease on pregnancy

Cardiovascular disease in pregnancy is associated with an increased incidence of preterm delivery and small-for-date babies

There is an increased incidence of congenital heart disease in the fetus when the parent has congenital heart disease; the risk to the fetus is more if the mother has congenital heart disease rather than the father.

Maternal medicines taken for cardiac disease can adversely affect the fetus. Thus, the use of warfarin-type oral anticoagulants can result in *warfarin embryopathy* if exposure occurs in the first trimester of pregnancy. Warfarin embryopathy is characterised by facio-skeletal malformations. The use of warfarin in the third trimester of pregnancy can result in excessive peripartum hemorrhage. A switch to heparin is advisable both in the first and in the last trimesters if anticoagulation is mandatory. Similiarly, thiazide diuretics, angiotensin-converting enzyme inhibitors and sodium nitroprusside are to be avoided in pregnancy.

Effect of pregnancy on cardiac disease

The fall in systemic vascular resistance and the resultant decrease in left ventricular afterload that occurs in pregnancy tend to ameliorate symptoms in subjects with regurgitant lesions (mitral or aortic), or with left to right shunts (VSD, ASD, PDA). Symptoms also improve in pregnant subjects with mitral valve prolapse (MVPS) or hypertrophic obstructive cardio-myopathy (HOCM). The increase in circulatory blood volume results in an increase in ventricular end-diastolic volume; this diminishes the degree of mitral valve prolapse in MVPS and the left ventricular outflow tract gradient in HOCM. Patients with pulmonic stenosis often have an uneventful pregnancy. In contrast, pregnant patients with aortic stenosis or mitral stenosis deteriorate due to the hemodynamic burden of pregnancy. Patients with pulmonary arterial hypertension due to primary pulmonary hypertension or due to Eisenmenger syndrome tolerate pregnancy very poorly, with very high maternal and fetal mortality rates being reported.

Certain cardiac diseases occur peculiarly with increased frequency during pregnancy. These include splenic artery aneurysms, dissection of the aorta, coarctation-related aortic rupture and deep venous thrombosis.

Peripartum cardiomyopathy

Peripartum cardiomyopathy is defined as the onset of myocardial dysfunction leading to congestive heart failure in the last trimester of pregnancy or upto six months postpartum, without prior evidence of any underlying cardiac disease. Most cases occur in the postpartum period, especially in the immediate postpartum period. It is more frequently seen in multiparous women, in older age groups and with 'twinning'. Increased dietary salt and the practice of lying on baked bricks have been implicated as probable causative factors in some African tribes. Recent evidence based on endomyo-cardial biopsy of subjects has suggested an etiologic role of viral myocarditis in this illness.

The clinical features of peripartum cardiomyopathy are very similar to that of idiopathic dilated cardiomyopathy with the additional presence of a peripartum state.

Treatment is with digoxin, diuretics, bedrest and dietary salt restriction.

The natural history of the disease is variable with upto half of the patients experiencing spontaneous improvement in the postpartum period. Failure to resolve after a pregnancy is an adverse prognostic factor for worsening of myocardial failure in subsequent pregnancies.

Pregnancy-induced Hypertension (PIH)

Normally pregnancy is associated with a fall in blood pressure (systolic and diastolic) reflecting a fall of systemic vascular resistance under the influence of vasodilatory progestagens and the low resistance placental circuit. The cut-off point for defining hypertension in the context of a pregnancy is, therefore, lower. Blood pressure equal to or greater than 140/90 mmHg is defined as hypertension in a pregnant subject. *Preeclampsia* or pregnancy-induced hyper-tension refers to the onset, during pregnancy, of

the *triad of edema, hypertension* and *proteinuria.* A previously hypertensive subject is said to manifest *superimposed preeclampsia* if there is an increase in blood pressure of >30mm systolic or >15mm diastolic as compared to initial blood pressures.

Pathophysiology The hypertension in pregnancy-induced hypertension is only one component of the triad. It is probably related to an imbalance between humoral vasoconstrictor and vasodilatory influences, with an increase in the former (principally, thromboxane A_2) and a decrease in the latter (prostacyclin, PGI_2). The proteinuria is related to a specific pathologic change in glomerular endothelial cells, *glomerular endotheliosis.* Edema is multi-factorial, being related to venous compression by the gravid uterus, an elevated hydrostatic pressure and a decrease in plasma oncotic pressure due to urinary protein loss.

Effect of hypertension on pregnancy
Pregnancy-induced hypertension is associated with an increased incidence of preterm labour, abruptio placentae and small-for-gestational-age babies. About a third of women with chronic hypertension develop superimposed pre-eclampsia on becoming pregnant.

Management Bed rest, judicious restriction of dietary salt, adoption of a left-lateral decubitus position and the appropriate use of antihypertensive drugs remain the cornerstone of therapy. There is some evidence to suggest that the use of aspirin in women who are at high risk of developing pregnancy-induced hypertension diminishes the incidence of this complication.

Regarding the use of antihypertensive agents in pregnancy, hydralazine, M-Dopa, labetalol and atenolol have been reported to be safe and free from any major side effects.

GLUCOSE INTOLERANCE STATES IN PREGNANCY

Women demonstrating abnormal carbohydrate metabolism in pregnancy, arbitrarily defined as a two-hour postprandial capillary blood glucose level greater than 120 mg/dl following a 100 g carbohydrate meal, have been diagnosed as manifesting *pregnancy-induced glucose intolerance.* This term is preferable to the term *gestational diabetes* as it avoids the negative psychological connotation of the latter label.

Effect of pregnancy on diabetes mellitus
In subjects with preexisting Type I diabetes mellitus, the early weeks of pregnancy are associated with accelerated starvation ketosis manifested by early morning ketonuria and an increased sensitivity to previously well-tolerated doses of insulin resulting in frequent hypoglycemic episodes. Later in pregnancy, this tendency is reversed with often an increased requirement of exogenous insulin. In patients with Type II diabetes mellitus, however, symptomatic hypoglycemia is rare. There is an overall increased risk of ketoacidosis. Established diabetic retinopathy or nephropathy may worsen during gestation.

Effect of diabetes mellitus on pregnancy
When glucose homeostasis is well-maintained, perinatal morbidity and mortality do not differ between diabetic and non-diabetic pregnant women. When maternal blood glucose is not well-controlled, infants of diabetic mothers are at increased risk of spontaneous abortion, congenital anomalies, macrosomia (leading to birth trauma), hypoglycemia, respiratory distress and hyperbilirubinemia.

Management When two-hour postprandial blood glucose values (after a 100 g carbohydrate meal) are in the 121–140 mg/dl range, dietary measures are advised; these include a caloric intake of 25–35 kcal/kg of ideal body weight, 40–50 per cent carbohydrate, 30 per cent fat and

20–30 per cent protein. With postprandial glucose values of 170 mg/dl or greater, insulin therapy is initiated.

EPILEPSY AND PREGNANCY

Effect of seizures on pregnancy

Most women with seizures can successfully have healthy babies (90 per cent). The risk of seizures in these children is about five times that in the general population (five per cent). This is not unacceptably high. However, women with associated mental retardation or neurological abnormalities besides seizures are more likely to have an inherited disorder with a high penetrance such as tuberous sclerosis. In such women, pregnancy may be discouraged. Two more considerations are whether the woman is physically, mentally and emotionally fit enough for the demanding task of motherhood, and whether the seizures are adequately controlled on a non-teratogenic drug.

Choice of contraception Oral contraceptives induce hepatic enzymes. They may alter the levels of some anticonvulsants such as phenytoin, phenobarbitone and sodium valproate. They can be used if this fact is kept in mind. Any other form of contraception can be used.

Timing of conception Ideally, the woman should have been seizure-free for at least two years. The anti-epileptic medication is tapered off and if she remains seizure-free for six months, (without drugs), she is advised that she can have a baby.

The next stratum of risk is in women who are seizure-free on drugs, but cannot stop the drugs. They should continue with the same drug and dose which controls their seizures.

Most women, despite a few seizures, also have healthy babies. However, their risk of obstetric complications (for example, abruptio placentae) and intrauterine growth retardation is higher. An episode of status epilepticus results in hypoxia and acidosis which is very dangerous for the fetus. Generalised tonic-clonic seizures are more dangerous than other types of seizures.

Choice of drug during pregnancy Trimethadione is the most teratogenic drug but is rarely used today. Sodium valproate definitely increases the risk of spina bifida. If a woman's seizures cannot be controlled with any other drug, ultrasound examination and alpha fetoprotein estimation should be done during pregnancy to screen for neural tube defects.

The three major drugs carbamazepine, phenytoin and phenobarbitone are reasonably safe. All three can cause minor cranio-facial abnormalities, nail hypoplasia and delayed development, a spectrum of abnormalities called the *fetal hydantoin syndrome.* Women with a high level of a hepatic enzyme (arene oxide) are more likely to have high blood levels of teratogenic metabolites of these three drugs. Carbamazepine is the safest of the three drugs (until five years ago it was thought to be totally safe); however, it is more costly and so compliance may be lower, especially if the patient is poor. It must, however, be remembered that seizures themselves are more teratogenic than the drugs. Overall, the risk of congenital malformations in infants born to epileptic mothers is about 6 per cent (three times the normal risk).

Effect of pregnancy on seizures In a third of patients, pregnancy has no effect on the frequency of seizures. In another third the frequency increases and in the rest it decreases. In the first trimester, drug doses may be missed due to nausea or fear of possible teratogenicity. Patients should be warned against missing doses. In the second trimester, drug levels tend to fall due to increased fluid retention (increased volume of distribution) and increased hepatic and renal clearance. Higher doses may, therefore, be required in some patients.

The newborn

Breast feeding should be encouraged as in all mothers. Babies born to mothers on high doses of phenobarbitone may show initial sleepiness, followed by 'withdrawal symptoms' of irritability and jitteriness. In rare cases a bleeding tendency can develop during the first day of life in neonates whose mothers are on phenytoin, carbamazepine or phenobarbitone. This can be corrected by vitamin K injection.

Seizures due to eclampsia are discussed in a separate chapter.

KEY CONCEPTS

- ➢ Asthma has no consistent effect on pregnancy. Conversely, pregnancy also has no consistent effect on asthma.
- ➢ Inflammatory bowel disease has no adverse effect on pregnancy (when controlled). Patients with inflammatory bowel disease have a milder course during pregnancy.
- ➢ The most common cause of jaundice in pregnancy is viral hepatitis. Benign recurrent intrahepatic cholestasis causes jaundice in the second trimester, is self resolving and tends to recur in subsequent pregnancies.
- ➢ Cardiac valvular regurgitant lesions ameliorate during pregnancy. Patients with severe valvular stenoses tolerate pregnancy poorly. Pregnant patients with primary pulmonary hypertension and Eisenmenger syndrome have a very high mortality. Pregnant patients with Marfan syndrome have an increased risk of aortic dissection.
- ➢ Blood pressure normally tends to fall during pregnancy. Hypertension during pregnancy carries an increased risk of preterm delivery, placental abruption, intrauterine growth retardation and stillbirth.
- ➢ Infants of diabetic mothers have an increased risk of congenital anomalies, macrosomia, respiratory distress, hyperbilirubinemia and hypoglycemia. During the first trimester, the pregnant diabetic may be at risk of starvation ketosis. Insulin requirement may increase in the third trimester.
- ➢ Pregnancy is well tolerated by patients with epilepsy. Sodium valproate is associated with embryopathy and should be avoided; carbamazepine, and phenytoin are relatively safe. Drug levels may change during pregnancy due to altered metabolism and this should be kept in mind by the treating physician.

21

Computers in Medicine

Computer-based knowledge systems

Medical informatics is the discipline concerned specifically with the acquisition, storage and communication of medical knowledge and data. Knowledge can be enclosed in a computer system to serve four important functions:

1. to serve as a teaching aid;
2. to serve as a medical decison-making aid;
3. to store facts as a 'knowledge-base';
4. to serve as a *hypertext* (explained below).

Teaching aids are computer-based systems that have a medical knowledge-base and programmes to frame and execute searches for solutions to problems. Medical decision aids also have a knowledge-base and search programmes with the difference that the latter are built around a patient model. These aids are based on the 'decision theory' outlined in Chapter 2. A decision tree is drawn with weightings added at each node to calculate the probability of the outcome along each branch or division. Medical knowledge-bases contain important information such as drug dosages, drug interactions, data on disease incidence or complication rates and even patient data. These can be stored on a central computer with remote access by links and on personal computers as well. Hypertexts are texts stored in such a fashion that rapid access is available to all pages, preceding chapters, glossaries and indices through computer links. Computer based knowledge systems thus provide a range of possibilities that even the best-equipped libraries are not able to provide.

Computer-based imaging techniques

Most current imaging techniques use computerised systems for digitising data and ensuring precision. Both the initial acquisition of images and subsequent measurement of data (for example, computer-based *edge detection algorithms*) utilise computers. Thus, computerised tomography, emission tomography, echocardiography, magnetic resonance imaging, digital subtraction angiograms all use computers that are built into the system.

Computer-based laboratory systems

Computers have become an important component of health economics. Thus, clinical laboratories use automated processing systems for analysing chemical and microbiologic data.

Automated information systems are also used for maintaining patient records.

Computer-based statistical analysis

Apart from maintaining detailed subject records and follow-ups, most clinical trials and investigations make use of computerised packages for statistical analysis.

Medical informatics and communications systems

Medical informatics is the field dealing with the use of medical information; this information can be communicated by several methods. Three such communication systems are *telemedicine,* the *electronic mail (e-mail)* and the *Internet.*

Telemedicine is a means by which patients can communicate with health care providers over long distances using two-way audio or two-way video means. Telemedicine may be used for the purposes of diagnosis, consultation or treatment. Telemedicine uses high-speed integrated services digital network telephones (image transfer systems) to transfer digitally compressed images between desktop computers; teleradiology is the branch in which radiologic images are communicated over lines whereas telepathology is the branch in which pathology slides are communicated between distant observers. A similar technology permits the transtelephonic transmission of ECGs to a physician remote from the patient.

The electronic mail is a method of exchanging short textual messages between computer users using a computer network. It is usually available in universities and hospitals. The internet is an open system of communication over an international electronic computer network. The World Wide Web (WWW) is one such software within the internet which provides users with easy and simple ways of accessing information. Certain medical journals, institutions and organisations have made documents available in hypertext format on the Internet which can be viewed globally; these documents can contain graphics, video and sound clips. Thus, a large number of technical, scientific and biomedical information sources can be accessed through the Internet.

KEY CONCEPTS

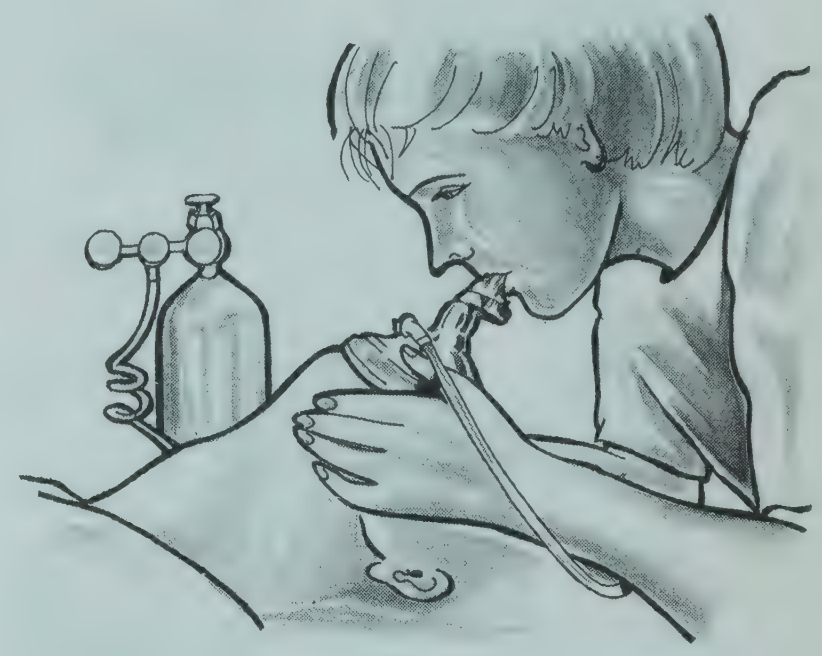
- Computers play a key role in medicine today. Potential areas where they are indispensable include the development of knowledge systems, computer-assisted imaging techniques (e.g., tomography), automated laboratory tests, and statistical analyses. Computers are also helping surgeons perform highly specialised stereotaxic neurosurgical procedures.
- The development of the Internet has revolutionised access to information from data sources. It has also enabled networking of centres across the globe.

Appendix A: Performance of procedures

a

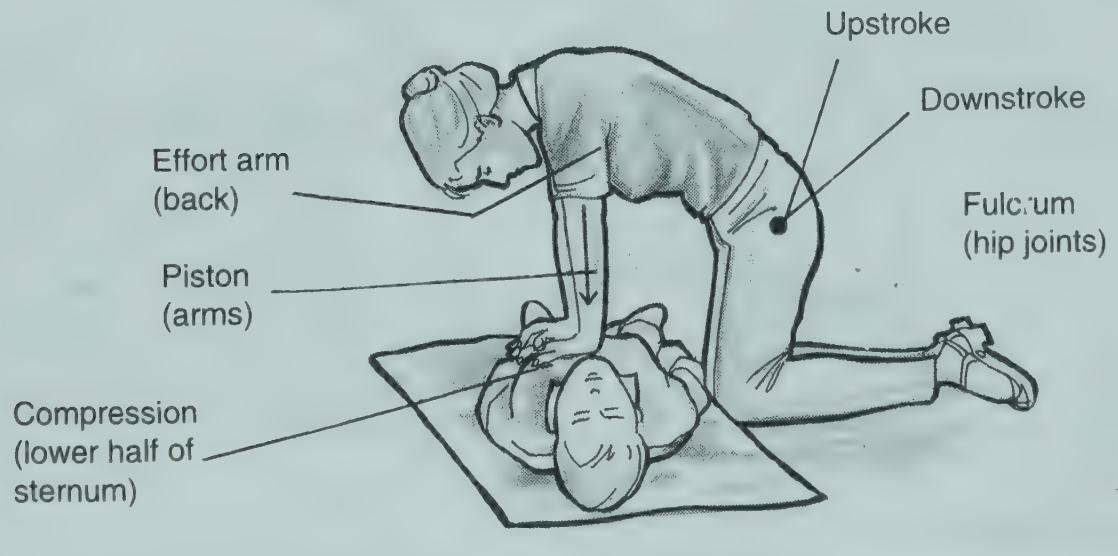
Absent respiratory effort

b



c

Absent pulse

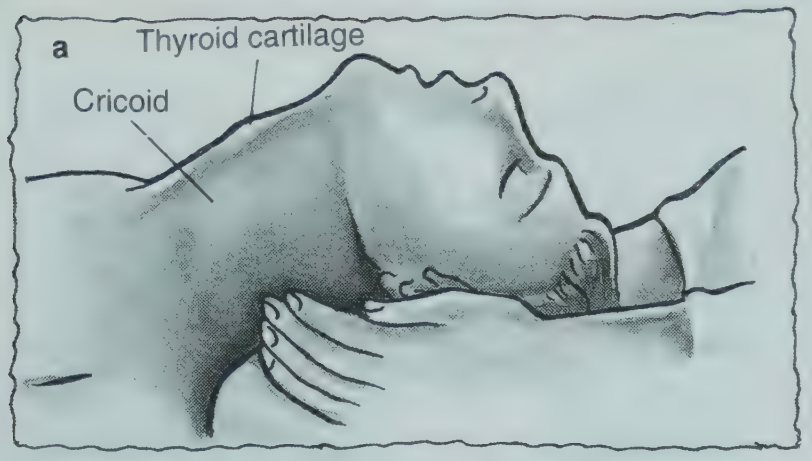


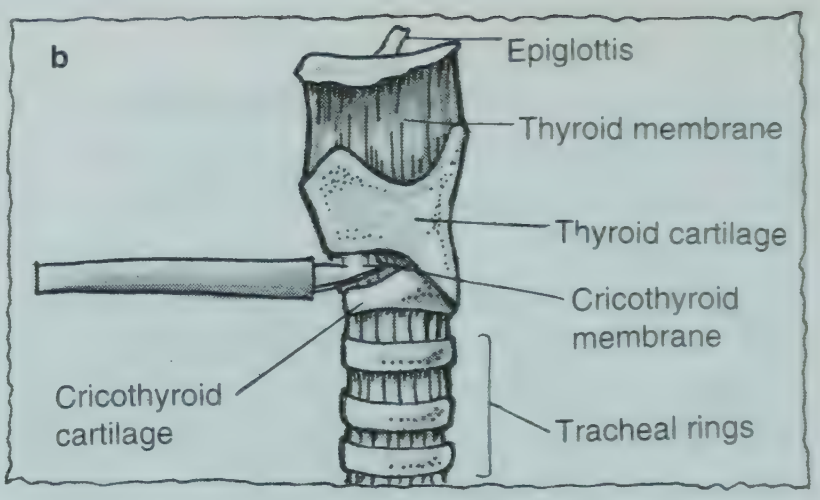
A. 1. Administering basic life support

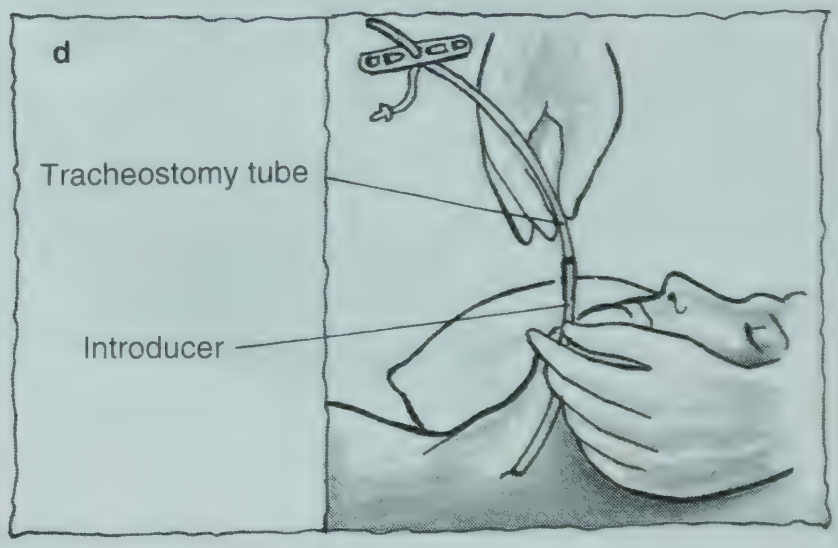
a. Proper method for opening the airway is with the head tilted and chin lifted to administer mouth to mouth respiration

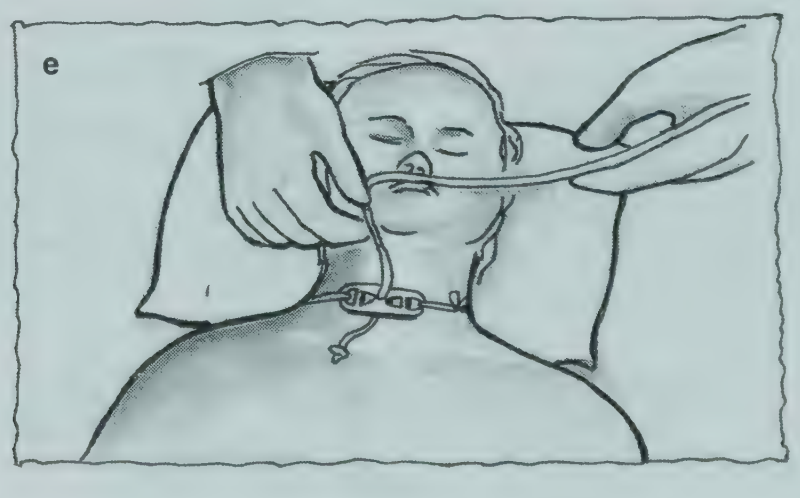
b. Proper technique for use of the pocket mask

c. Proper technique for chest compressions (uses principle of a lever). Note forearm and arm are straight (elbows extended). The recommended compression is 80–100 per minute. Fifteen chest compressions are performed before ventilating twice when there is a single rescuer. Palpate the carotids for detecting a pulse every two minutes.









A. 2 Performing a tracheostomy

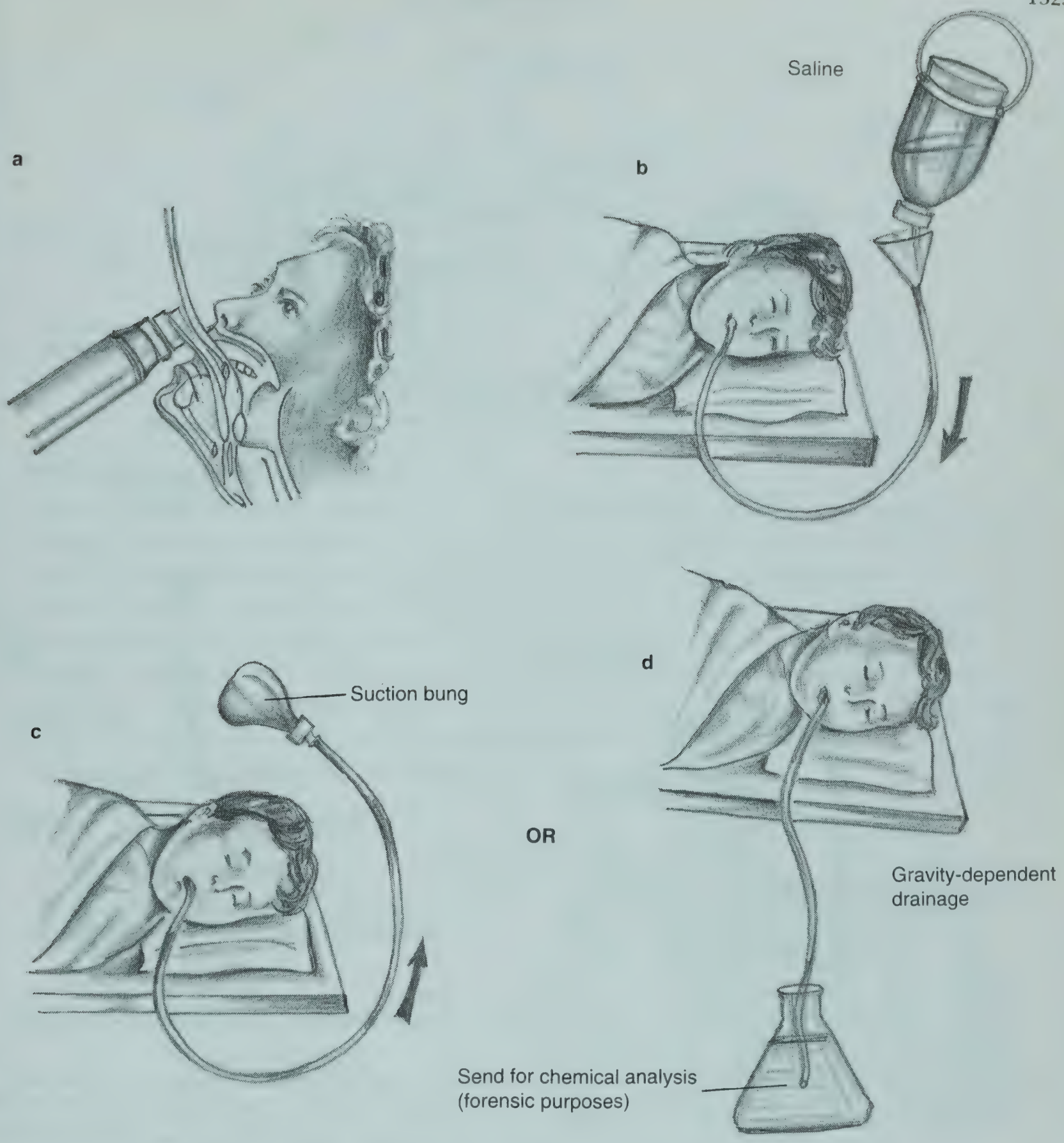
a. The patient is placed in the supine position with the head and neck fully extended. Palpate the thyroid and cricoid cartilages.

b. Diagram to show the position of the cricothyroid membrane. Nick the cricothyroid membrane with a scalpel blade.

c. The blunt plastic introducer is passed through the incision and directed down into the trachea following the specially designed curvature.

d. The tracheostomy tube is 'railroaded' down the introducer and into the trachea. 'Railroading' refers to introducing the tube 'over' the introducer.

e. With one hand steadying the tracheostomy tube, the introducer is gently withdrawn, and the suction catheter used to aspirate sputum and any blood from the trachea.

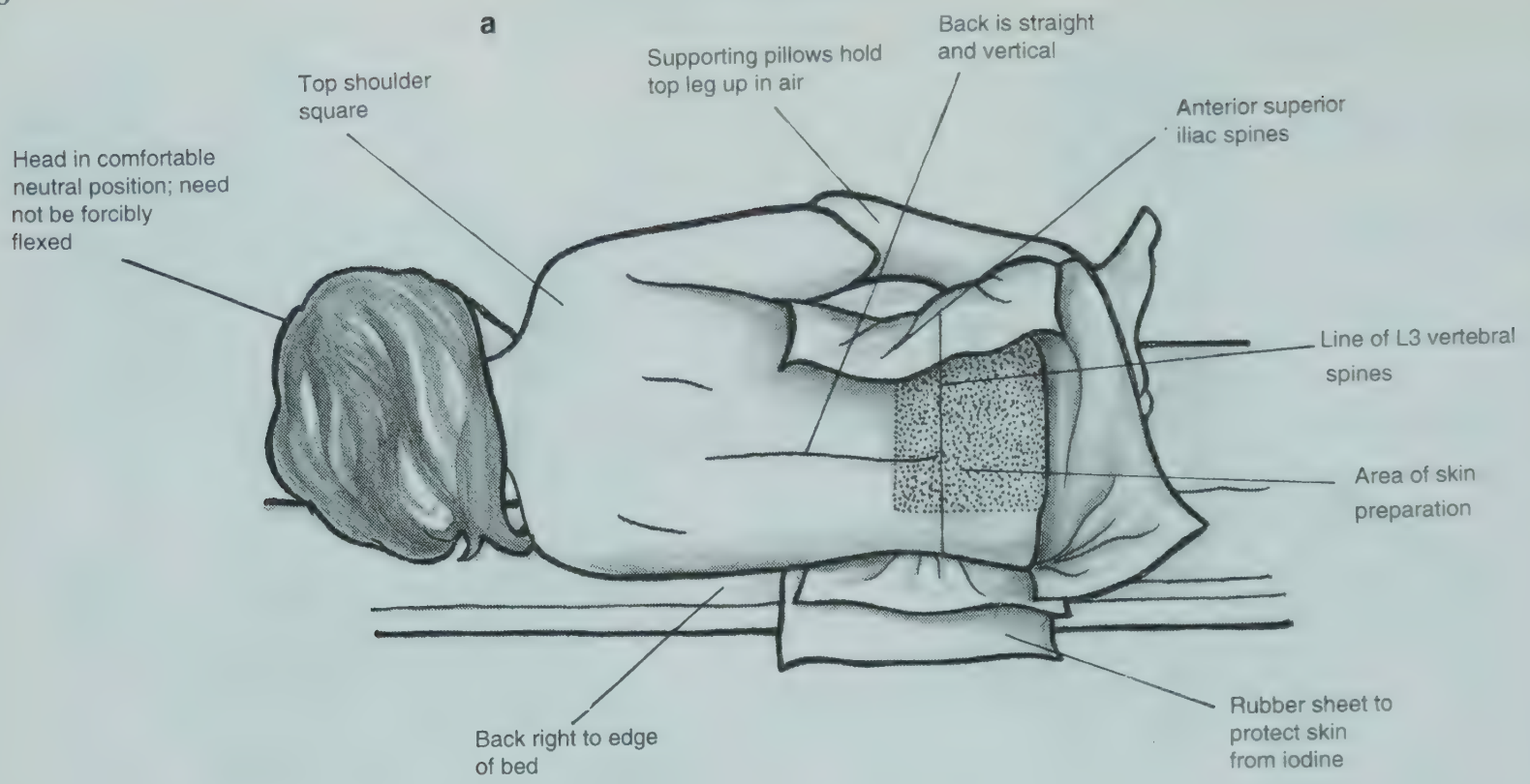


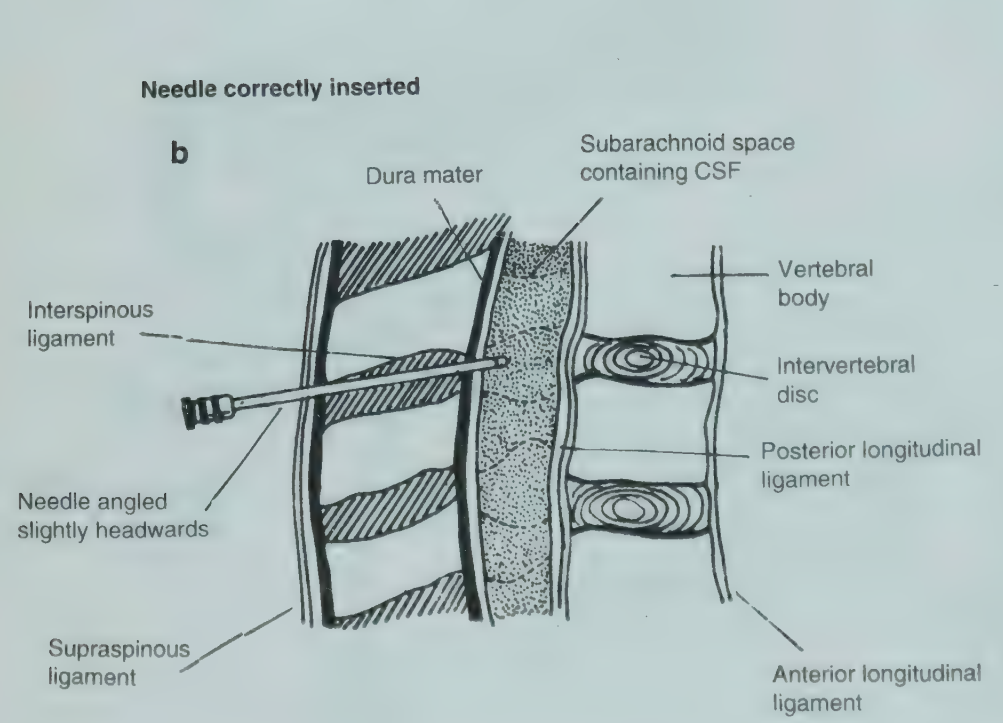
A. 3. Performing a gastric lavage in a patient with suspected poisoning

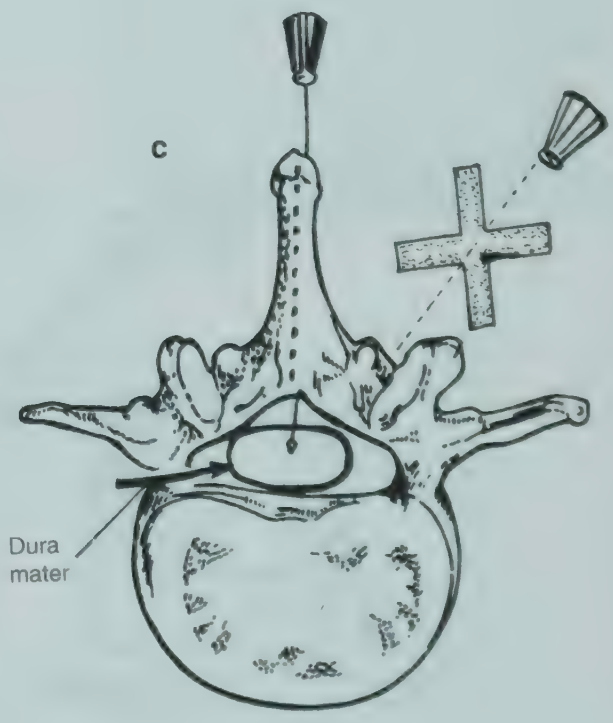
a. Strongly consider endotracheal intubation prior to lavage if the patient has a decreased or absent gag reflex.

b. and c. Lavage is performed by inserting a large-bore, semirigid orogastric tube. Administer several litres of room-temperature saline solution until the lavage fluid runs clear without particles. 200 ml aliquots of fluid can be used. Avoid lavage if poisoning is due to corrosives or hydrocarbons.

d. Send for chemical analysis (forensic purposes).

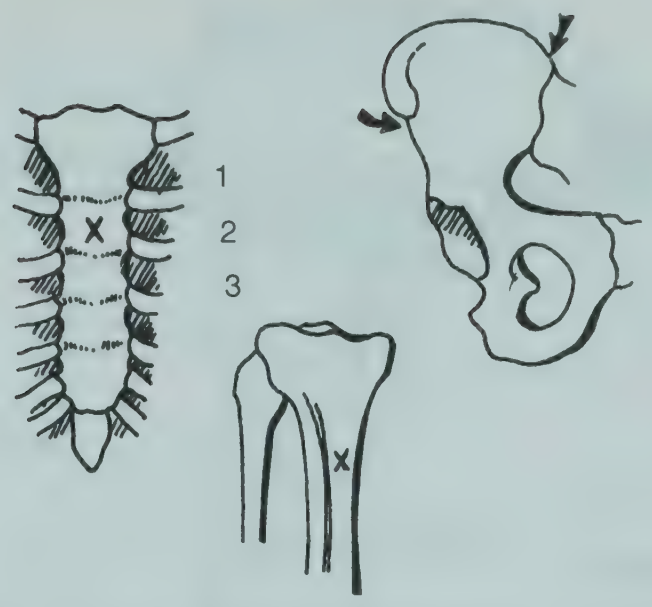






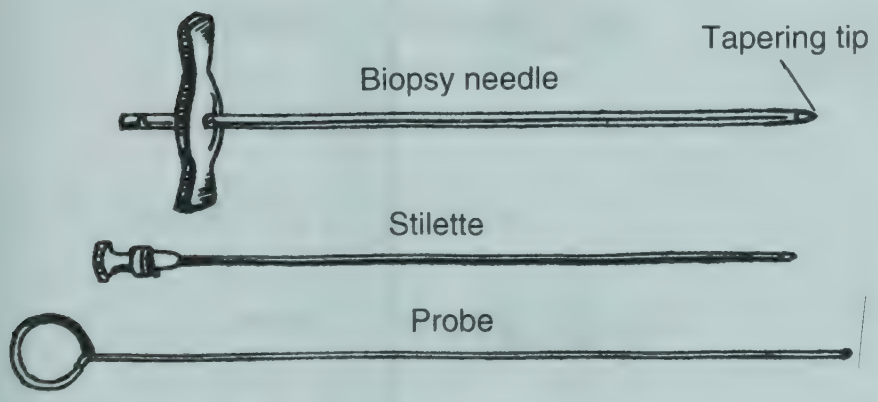
A. 4. Performing a lumbar puncture

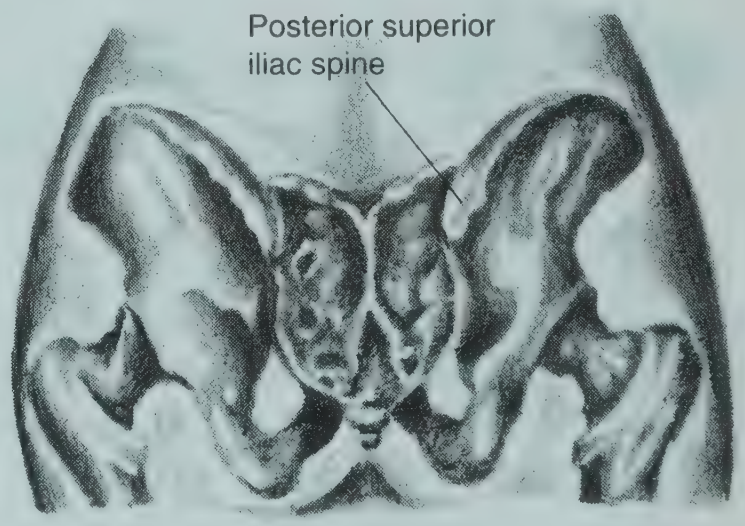
Position the patient correctly as shown (a). Clean the skin with antiseptics and position the sterile drapes. Palpate the anterior superior iliac spine and identify the spinal interspace perpendicular to it (the L3–4 interspace). After anesthetising the skin, introduce the lumbar puncture needle (usually 19 or 20 gauge) through the space with the stilette fully inside and the bevel in the sagittal plane and pointing upwards. Advance the needle forwards slightly pointing to the head. At about 4–6 cm, a firmer resistance is felt (ligamentum flavum). An extra push will result in a feeling of 'give' as the dura is breached. Withdraw the stillette and the cerebrospinal fluid will drip if the needle is in the subarachnoid space (b). If no fluid emerges rotate the needle to remove any flap of dura lying against the bevel). If yet again no fluid emerges, reinsert stilette and advance slowly, withdrawing the stilette to check for fluid. A dry tap is usually the result of a faulty technique (c).



A. 5. Perfoming bone marrow aspiration

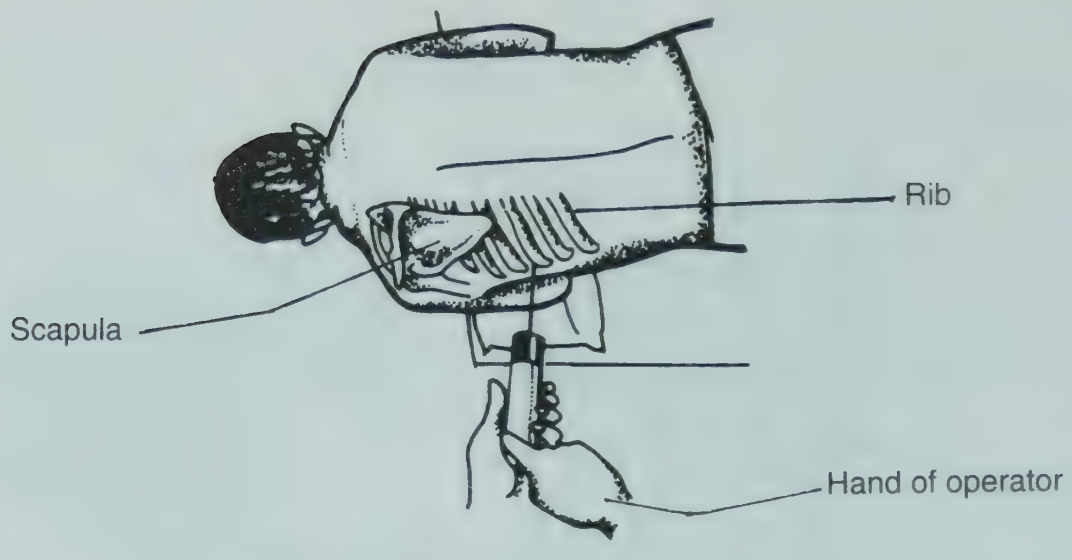
A bone marrow aspiration needle is used and the ideal site is the iliac crest at the posterior superior iliac spine. In children below one year, the anteromedial surface of the tibia can be used. The sternal site is associated with maximum hazard. With the patient prone, the area is cleaned, dried and anesthetised. The bone marrow aspiration needle is inserted through the skin, subcutaneous tissue and cortex of the bone with a twisting motion. Penetration of the cortex is associated with a feeling of 'partial give'. The stilette is removed and the hub attached to a 10 mm syringe. Suction is applied and about 0.2–0.5 ml of fluid is aspirated. Remove the needle thereafter and apply local pressure to the bony site to ensure hemostasis. The contents of the syringe are discharged onto a glass slide.





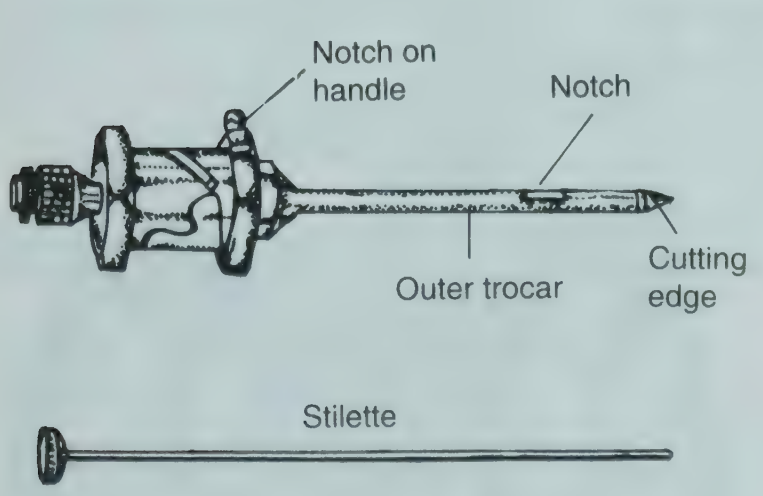
A. 6. Performing a bone marrow biopsy

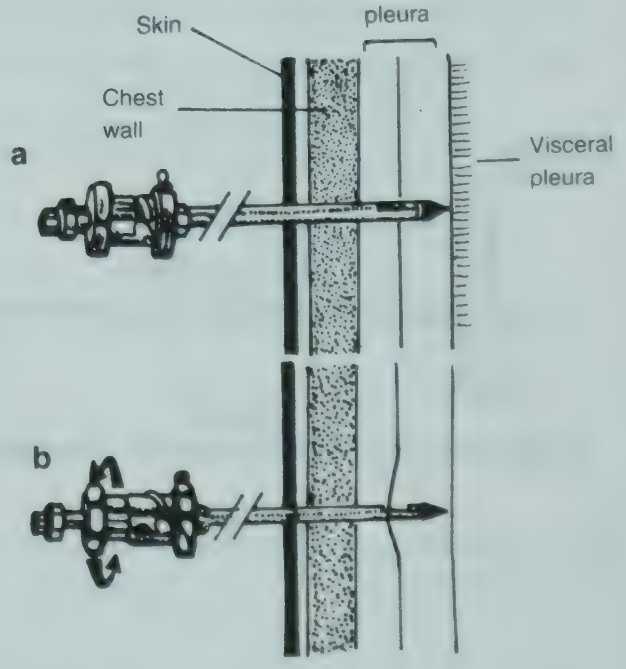
The Jamshidi biopsy needle is used and the site of choice is the posterior superior iliac spine. After preparing the skin and positioning the patient (as for a marrow aspiration), the Jamshidi needle is inserted with the stilette in place through the skin and subcutaneous tissue into the cortex of the bone with a twisting motion. Once the penetration of the cortex is felt, the stilette is removed and the needle advanced further for 2–3 cm. The needle is then withdrawn using the same twisting motion. The core of the marrow is removed by inserting the probe through the cutting tip of the needle and extruding the biopsy through the hub of the Jamshidi needle.



A. 7. Performing a pleural aspiration

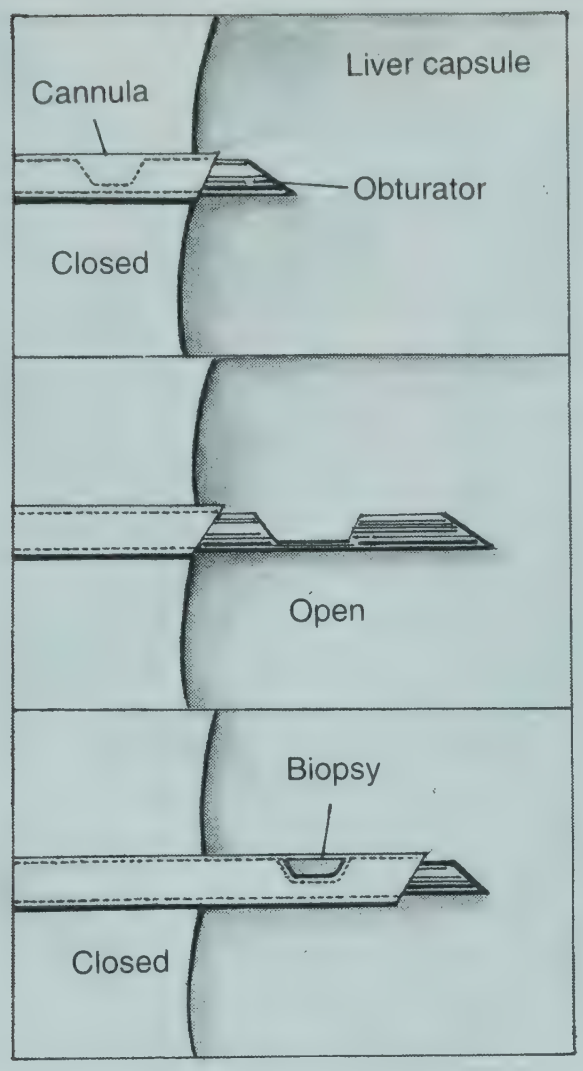
The patient is positioned sitting in bed, leaning forward with arms folded before him on a 'cardiac' table. The site of puncture is judged from the PA and lateral chest X-ray films. The posterior chest wall below and medial to the scapula is a favoured site for non-loculated effusions. After cleaning, draping and anesthetising the skin, the pleural aspiration needle is introduced along the lower part of the intercostal space (to avoid the neurovascular bundle which lies along the inferior border of the rib above). The needle is connected to a 20 m syringe through a 3-way stopcock. When the needle enters the pleural space, pleural fluid appears in the syringe on suction.

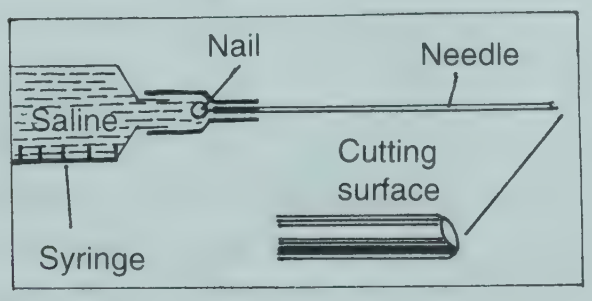




A. 8. Performing a pleural biopsy

The Abrams needle has a notch on the handle that faces the same way as the notch on the trocar. The outer tube (trocar) has an opening into which a fold of pleura is impacted. When the inner tube is advanced, the pleura which is impacted is cut by the cutting edge of the inner tube and is retained within the instrument. The notch on the handle is always kept facing medially and never upwards (to avoid damage to the intercostal neurovascular bundle). The needle is inserted (a), and the grip of the inner tube turned clockwise to take the specimen (b).

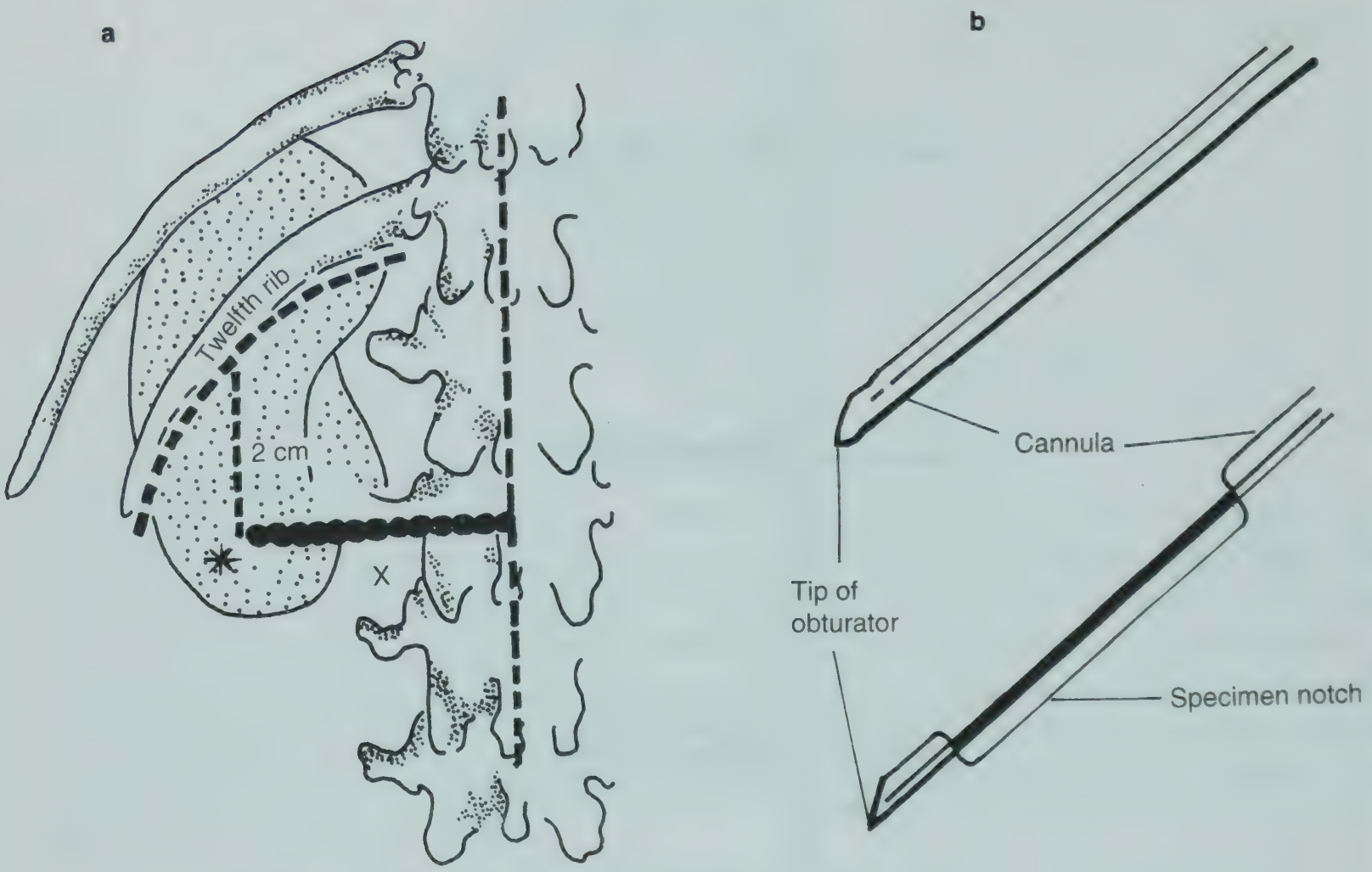




A. 9. Performing a liver biopsy

a. The patient lies supine and the area of skin in the right 6th intercostal space is cleaned, draped and anesthetised in the mid-axillary line. The patient is asked to hold his breath in expiration. Thrust the 'trucut' needle cannula closed over the obturator an inch into the liver (i). Advance the obturator holding the cannula still (ii). Advance the cannula over the obturator and withdraw the whole needle (iii) with the cannula closed over the obturator.

b. In the other technique, a Menghini needle is used. A small nail is placed in the proximal end of the needle to prevent aspiration of the biopsy specimen into the attached syringe. The syringe is filled with saline and the needle fixed onto its nozzle. The needle is then advanced into the liver through the area of skin that has been cleaned, draped and anesthetised. One ml saline is expelled from the needle to remove debris. Suction is applied to the syringe while the needle is further advanced 3–4 cm into the liver and then withdrawn. The nail is removed and the specimen pushed out of the end of the blunt trocar onto a petri dish. The specimen is removed and immersed in formalin/saline.

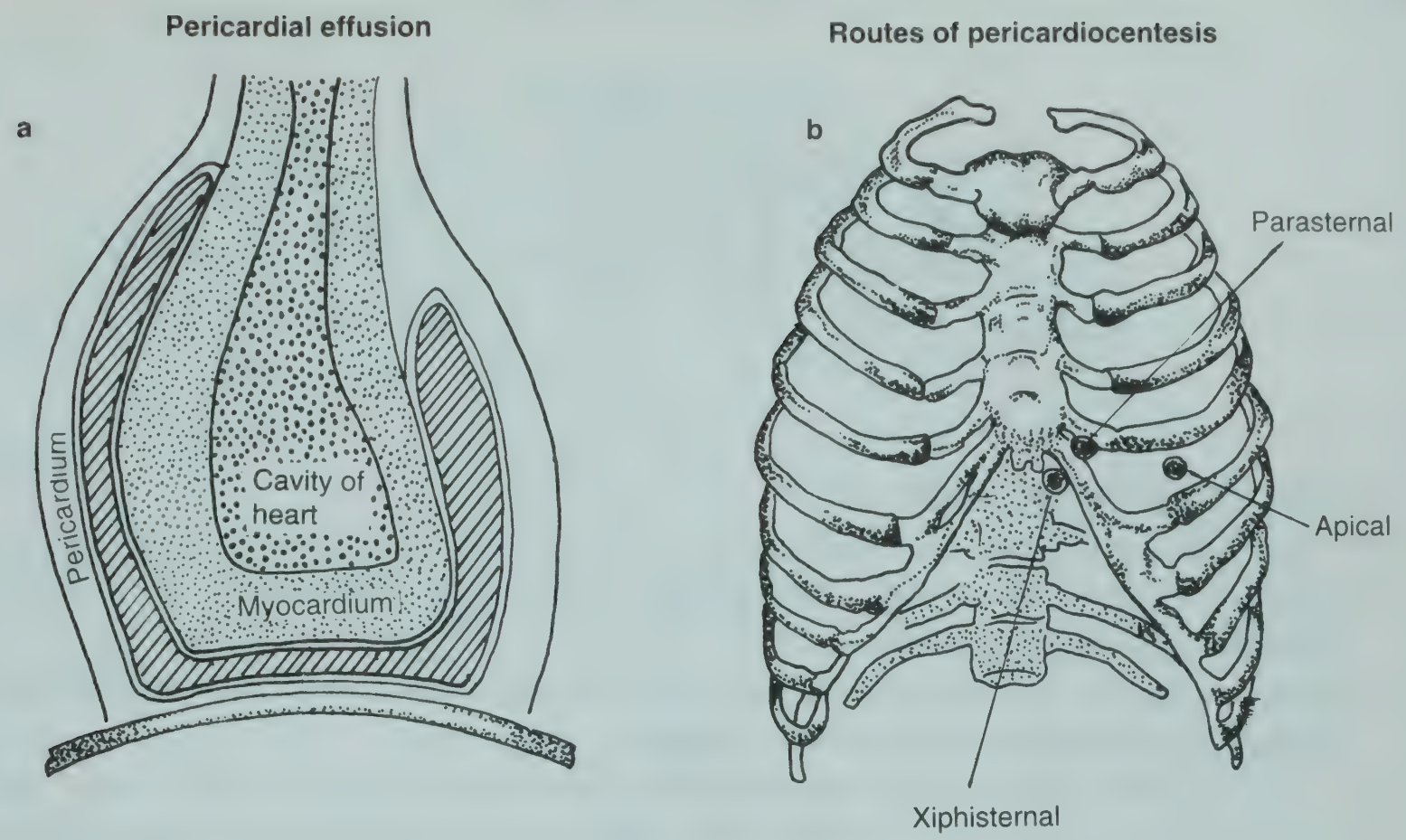


A. 10. Performing a kidney biopsy

The procedure is ideally performed only by an experienced physician and und ultrasonographic guidance. The patient is placed prone on a firm surface with her arr abducted and forearms beside her head. A rolled towel about 10 cm in diameter is plac under the patient's abdomen, between the rib cage and pelvis.

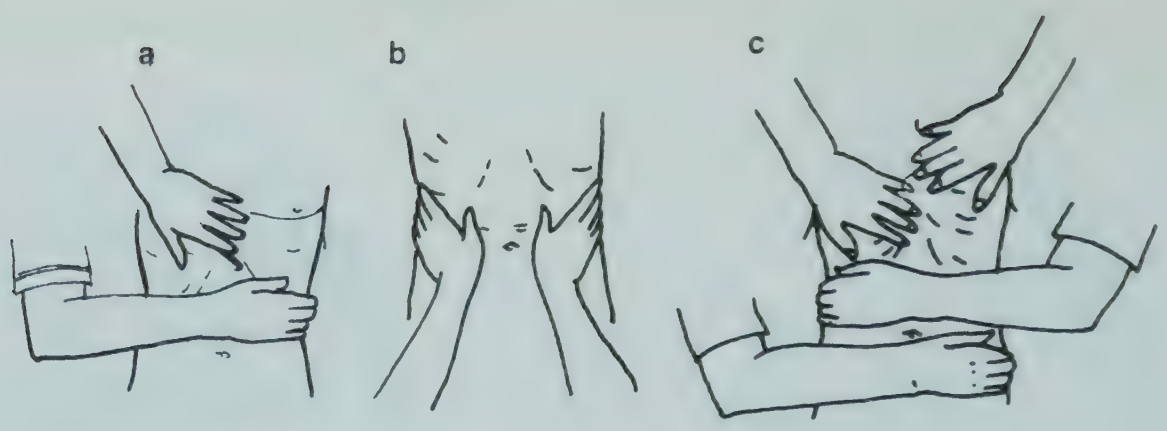
The preferred side is the centre of the lower pole of the left kidney. If an intravenous urogra is available, measure the distance of the lower pole from the lumbar spinous process (Palpate the patient's twelfth rib and the tip of the lumbar spinous process and mark on t patient's skin. Draw a line vertically downwards from the twelfth rib at a distance 'x' cm fr the spine. Choose a site along this line 2 cm below the lower border of the twelfth rib (Clean, drape and anesthetise the skin. Use a 20 gauge 'exploring needle' inserted into t lumbar muscles at the point* progressively (5 mm at a time) till a swing of the needle is not with each respiration. Inject local anesthetic along the track and withdraw the needle (af noting the depth of penetration). Insert the 'trucut' needle (with cannula closed over t obturator) (b) till the tip reaches the approximate depth and a swing is noticed. Ask t patient to hold her breath, tap the obturator handle in, push the cannula down the obtura and withdraw the needle with cannula closed over the obturator.

Pulse and blood pressure are monitored during and after the procedure by an assistant.



A. 11. Performing a pericardiocentesis

The safest route is the xiphisternal route. The patient sits in bed at an angle of 45° and is undressed to the waist. Clean the precordium and epigastrium with antiseptic solution and drape the surrounding area. An 18 gauge needle connected to a 20 ml syringe (via a three-way tap) is used for pericardiocentesis. The needle is connected to lead V of the ECG by a sterile alligator clip. Ideally, the procedure is done under echocardiographic or fluoroscopic guidance. The needle is aimed upwards and backwards towards the spine at an angle of 45° to the skin. Aspirate the fluid and send for analysis. If the needle touches the myocardium, jerks can be felt with each heart beat and the monitoring lead shows elevation of the ST segment. Withdraw the needle a little if this happens. Blood pressure and cardiac rhythms are monitored throughout the procedure by an assistant.

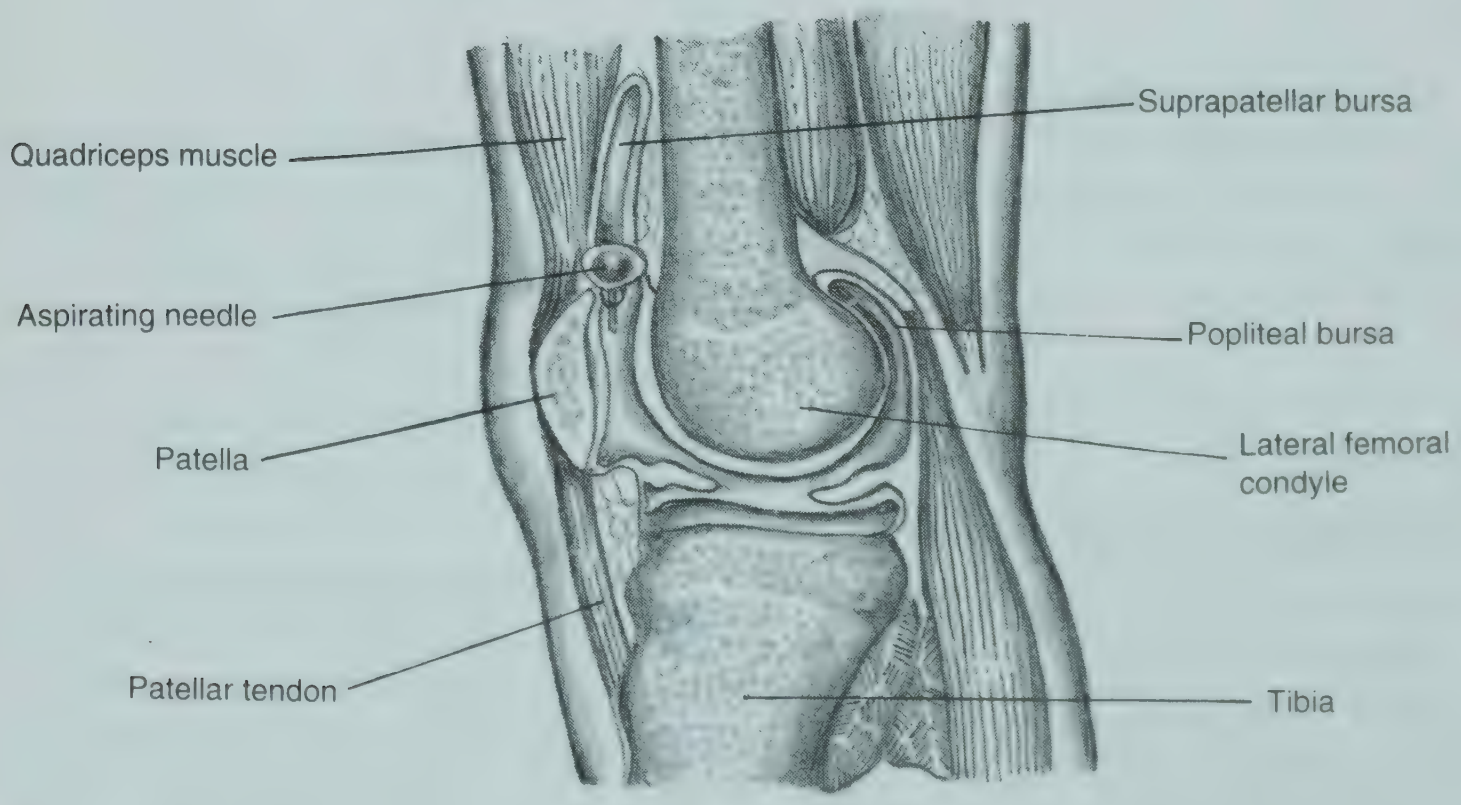


A. 12. Performing chest physiotherapy

a. The physician's hands are placed just below the ribs and as the patient coughs the physicia pushes upwards and inwards, taking care not to press down on to the abdomen, thu producing an effective cough.

b. Help can also be given by the physician if the forearm is placed under the lower ribs, pushin upwards and forwards as the patient coughs.

c. A heavily built patient or one with excessive pulmonary secretions will be more effectivel treated by two people, one on either side of the patient and each having one arm below th ribs and the other on the upper chest wall. The patient's relatives can be taught to do thi effectively.



A. 13. Aspirating a joint

The extremity should be held fairly straight and the needle inserted from a latera suprapatellar direction. Slide the needle under the midpoint of the patella, between it and th femur. Aspirate the synovial fluid. The accessible space behind the patella communicates wit the rest of the knee joint as well as with the popliteal bursa posteriorly.

Appendix B
Biochemical Values

1. Blood, plasma or serum values

Determination	*Reference range*	
	Conventional	*SI*
1. Amylase	0–130 U/litre 4–25 units/ml	0–2.17 μkat/litre 4–25 arb. unit
2. Bilirubin	Direct: upto 0.4 mg/100 ml Total: upto 1.0 mg/100 ml	upto 7.0 μmol/litre upto 17.0 μmol/litre
3. Blood volume	8.5–9.0% of body weight in kg	80–85 ml/kg
4. Calcium	8.5–10.5 mg/100 ml (slightly higher in children)	2.1–2.6 mmol/litre
5. Ceruloplasmin	27–37 mg/100 ml	1.8–2.5 μmol/litre
6. Chloride	100–106 mEq/litre	100–106 mmol/litre
7. CK isoenzymes	5% MB or less	
8. Copper	Total: 100–200 μg/100 ml	16–31 μmol/litre
9. Creatine kinase (CK)	Female: 10–79 U/litre Male: 17–148 U/litre	167–1317 nmol. sec^{-1}/litre 283–2467 nmol. sec^{-1}/litre
10. Creatinine	0.6–1.5 mg/100 ml	53–133 μmol/litre
11. Glucose	Fasting: 70–110 mg/100 ml	3.9–5.6 mmol/litre
12. Iron	50–150 μg/100 ml (higher in males)	9.0–26.9 μmol/litre
13. Iron-binding capacity	250–410 μg/100 ml	44.8–73.4 μmol/litre
14. Lactic acid	0.6–1.8 mEq/litre	0.6–1.8 mmol/litre
15. Lactic dehydrogenose	45–90 U/litre	750–1500 nmol. sec^{-1}/litre
16. Lead	50 μg/100 ml or less	upto 2.4 μmol/litre
17. Lipase	2 units/ml or less	upto 2 arb. unit
18. Lipids: cholesterol : triglyceride	120–220 mg/100 ml 40–150 mg/100 ml	3.10–5.69 mmol/litre 0.4–1.5 g/litre
19. Magnesium	1.5–2.0 mEq/litre	0.8–1.3 mmol/litre
20. Osmolality	280–296 mOsm/kg water	280–296 mmol/kg
21. Oxygen saturation (arterial)	96–100%	0.96–1.00
22. PCO_2	35–45 mmHg	4.7–6.0 kPa

Determination	*Reference range*	
	Conventional	*SI*
23. pH	7.35–7.45	7.35–7.45
24. PO_2	75–100 mmHg (depending on age) while breathing room air. Above 500 mmHg while on 100% O_2	10.0–13.3 kPa
25. Phosphatase (acid)	Male–Total: 0.13–0.63 sigma U/ml Female–Total: 0.01–0.56 sigma U/ml Prostatic: 0–0.5 Fishman Lerner U/100 ml	36–175 nmol. sec^{-1}/litre 2.8–156 nmol. sec^{-1}/litre 0–90 nkat/litre
26. Phosphatase (alkaline)	13–39 U/litre; infants and adolescents upto 104 U/litre	217–650 nmol. sec^{-1}/litre; upto 1.2 μmol. sec^{-1}/litre
27. Phosphorus (inorganic)	3.0–4.5 mg/100 ml (infants in first year upto 6.0 mg/100 ml)	1.0–1.5 mmol/litre
28. Potassium	3.5–5.0 mEq/litre	3.5–5.0 mmol/litre
29. Protein: Total	6.0–8.4 g/100 ml	60–84 g/litre
Albumin	3.5–5.0 g/100 ml	35–50 g/litre
Globulin	2.3–3.5 g/100 ml	23–35 g/litre
Electrophoresis	(% of total protein)	
Albumin	52–68	
Globulin:		
$Alpha_1$	4.2–7.2	
$Alpha_2$	6.8–12	
Beta	9.3–15	
Gamma	13–23	
30. Pyruvic acid	0–0.11 mEq/litre	0–0.11 nmol/litre
31. Transaminase, SGOT (aspartate aminotransferase, AST)	7–27 U/litre	117–450 nmol. sec^{-1}/litre
32. Transaminase, SGOT (alanine aminotransferase, ALT)	1–21 U/litre	17–350 nmol. sec^{-1}/litre
33. Urea nitrogen (BUN)	8–25 mg/100 ml	2.9–8.9 mmol/litre
34. Uric acid	3.0–7.0 mg/100 ml	0.18–0.42 mmol/litre

2. Urine values

Determination	*Reference range*	
	Conventional	*SI*
1. Amylase	24–76 units/ml	24–76 arb. unit
2. Calcium (24 hour)	300 mg/day or less	7.5 mmol/day or less
3. Catecholamines	Epinephrine: under 20 μg/day Norepinephrine: under 100 μg/day	< 109 nmol/day < 590 nmol/day
4. Copper	0–100 μg/day	0–1.6 μmol/day
5. Coproporphyrin	50–250 μg/day children under 80 lb (36 kg): 0–75 μg/day	80–380 nmol/day 0–115 nmol/day
6. Creatine	Under 100 mg/day or less than 6% of creatinine In pregnancy: upto 12% In children under 1 year: may equal creatinine In older children: upto 30% of creatinine	< 0.75 mmol/day
7. Creatinine	15–25 mg/kg of body weight/day	0.13–0.22 $mmol.kg^{-1}$/day
8. 5-hydroxyindole acetic acid	2–9 mg/day (women lower than men)	10–45 μmol/day
9. Protein: Quantitative	< 150 mg/24 hours	< 0–0.15 g/day
10. Steroids:		

a. 17-ketosteroids (per day)	*Age*	*Male*	*Female*	*Male* (μmol/day)	*Female* (μmol/day)
	10	1–4 mg	1–4 mg	3–14	3–14
	20–40	6–21 mg	4–16 mg	21–73	14–56
	50	5–18 mg	3–9 mg	17–62	10–31
	70	2–10 mg	1–7 mg	7–35	3–24

b. 17-hydroxysteroids	3–8 mg/day (women lower than men)	8–22 μmol/day as tetrahydrocortisol
11. Urobilinogen	upto 1.0 Ehrlich U	to 1.0 arb. unit
12. Uroporphyrin	0–30 μg/day	< 36 nmol/day
13. Vanillylmandelic acid (VMA)	upto 9 mg/24 hours	upto 45 μmol/day

3. Special endocrine tests

I. Steroid hormones

Determination	*Reference range*	
	Conventional	*SI*
1. Aldosterone	Excretion: 5–19 μg/24 hours	14–53 nmol/day
	Supine: 48 ± 29 pg/ml	133 ± 80 pmol/litre (fasting, at rest, normal diet)
	Upright (2 hours): 65 ± 23 pg/ml	180 ± 64 pmol/litre (normal diet)
	Supine: 107 ± 45 pg/ml	279 ± 125 pmol/litre (fasting, at rest 110–mEq sodium diet)
	Upright (2 hours): 239 ± 123 pg/ml	663 ± 341 pmol/litre (110–mEq sodium diet)
	Supine: 175 ± 75 pg/ml	485 ± 208 pmol/litre (fasting, at rest 10–mEq sodium diet)
	Upright (2 hours): 532 ± 228 pg/ml	1476 ± 632 pmol/litre (10–mEq sodium diet)
2. Cortisol	8 a. m.: 5–25 μg/100 ml	0.14–0.69 μmol/litre
	8 p.m.: Below 10 μg/100 ml	0–0.28 μmol/litre
	4 hour ACTH test: 30–45 μg/100 ml	0.83–1.24 μmol/litre
	Overnight suppression test: below 5 μg/100 ml	0.14 nmol/litre
	Excretion: 20–70 μg/24 hours	55–193 nmol/day
3. Dehydroepi-androsterone (DHEA)	Male: 0.5–5.5 ng/ml Female: 1.4–8.0 ng/ml 0.3–4.5 ng/ml (postmenopausal)	1.7–19 nmol/litre 4.9–28 nmol/litre (adult) 1.0–15.6 nmol/litre (postmenopausal)
4. Dehydroepiandro-sterone sulphate (DHEAS)	Male: 151–446 μg/100 ml Female: 84–433 μg/100 ml 1.7–177 μg/100 ml (postmenopausal)	3.9–11.4 μmol/litre 2.2–11.1 μmol/litre (adult) 0.04–4.5 μmol/litre (postmenopausal)
5. 11-Deoxycortisol	Responsive: over 7.5 μg/100 ml (8 a.m. sample after 2.5 g metyrapone at midnight)	> 0.22 μmol/litre

Determination	*Reference range*	
	Conventional	*SI*
6. Estradiol	Male: < 50 pg/ml	< 184 pmol/litre
	Female: 23–361 pg/ml (adult)	84–1325 pmol/litre
	< 30 pg ml (postmenopausal)	< 110 pmol/litre
	< 20 pg ml (prepubertal)	< 73 pmol/litre
7. Progesterone	Male: < 1.0 ng/ml	< 3.2 nmol/litre
	Female: 0.2–0.6 ng/ml (follicular phase)	0.6–19 nmol/litre (follicular phase)
	0.3–3.5 ng/ml (midcycle peak)	0.95–11 nmol/litre (midcycle peak)
	6.5–32.2 ng/ml (postovulatory a.m. sample)	21–102 nmol/litre (post-ovulatory a.m. sample)
8. Testosterone	Adult male: 300–1100 ng/100 ml	10.4–38.1 nmol/litre
	Adolescent male: Over 100 ng/100 ml	> 3.5 nmol/litre
	Female: 25–90 ng/100 ml	0.87–3.12 nmol/litre
II. Polypeptide hormones		
1. Adrenocorticotropin (ACTH)	15–70 pg/ml	3.3–15.4 pmol/litre
2. Calcitonin	Male: 0–14 pg/ml	0–4.1 pmol/litre
	Female: 0–28 pg/ml	0–8.2 pmol/litre
	> 100 pg/ml in medullary carcinoma	> 29.3 pmol/litre
3. Follicle-stimulating hormone (FSH)	Male: 3–18 mU/ml	3–18 arb. unit
	Female: 4.6–22.4 mU/ml (pre- or postovulatory)	4.6–22.4 arb. unit (pre- or postovulatory)
	13–41 mU/ml (midcycle peak)	13–41 arb. unit (midcycle peak)
	30–170 mU/ml (postmenopausal)	30–170 arb. unit (postmenopausal)
4. Insulin	6–26 μU/ml	43–187 pmol/litre
5. Luteinising hormone (LH)	Male: 3–18 mU/ml	
	Female: 2.4–34.5 mU/ml (pre- or postovulatory)	2.4–34.5 arb. unit (pre- or postovulatory)
	43–187 mU/ml (midcycle peak)	43–187 arb. unit (midcycle peak)
	30–150 mU/ml (postmenopausal)	30–150 arb. unit postmenopausal)
6. Parathyroid hormone	< 25 pg/ml	< 2.94 pmol/litre
7. Prolactin	2–15 ng/ml	0.08–6.0 nmol/litre
8. Renin activity	Supine: 1.1 ± 0.8 ng/ml/hr	0.9 ± 0.6 nmol/l/h (normal diet)
	Upright: 1.9 ± 1.7 ng/ml/hr	1.5 ± 1.3 nmol/l/h (normal diet)

III. Thyroid hormones

Determination	*Reference range*	
	Conventional	*SI*
1. Thyroid stimulating hormone (TSH)	0.5–5.0 μU/ml	0.5–5.0 arb. unit
2. Thyroxine binding globulin capacity	15–25 μg T_4/100 ml	193–322 nmol/litre
3. Total triiodothyronine (T_3)	75–195 ng/100 ml	1.16–3.00 nmol/litre
4. Reverse triiodothyronine (rT_3)	13–53 ng/ml	0.2–0.8 nmol/litre
5. Total thyroxine by RIA (T_4)	4–12 μg/100 ml	52–154 nmol/litre
6. T_3 resin uptake	25–35%	0.25–0.35
7. Free thyroxine index (FT_4I)	1–4	–

4. Hematologic values

1. *Coagulation factors*		
a. Factor I (fibrinogen)	0.15–0.35 g/100 ml	4.0–10.0 μmol/litre
b. Factor II (prothrombin)	60–140%	0.60–1.40
c. Factor VIII (antihemophilic globulin)	50–200%	0.50–2.00
2. *Coagulation screening tests:*		
a. Bleeding time	3–9.5 minutes	180–570 seconds
b. Prothrombin time	Less than 2 seconds deviation from control	Less than 2 seconds deviation from control
c. Partial thromboplastin time (activated)	25–38 seconds	25–38 seconds
d. Whole-blood clot lysis	No clot lysis in 24 hours	0/day

Determination	*Reference range*	
	Conventional	*SI*
3. *Fibrinolytic studies:*		
a. Fibrinogen split products	Negative reaction at >1:4 dilution	0 (at 1:4 dilution)
b. Thrombin time	Control ± 5 seconds	Control ± 5 seconds
c. 'Complete' blood count:		
i. Hematocrit	Male: 45–52% Female: 37–48%	Male: 0.45–0.52 Female: 0.37–0.48
ii. Hemoglobin	Male: 13–18 g/100 ml Female: 12–16 g/100 ml	Male: 8.1–11.2 mmol/litre Female: 7.4–9.9 mmol/litre
iii. Leukocyte count	4300–10,800/mm^3	4.3–10.8 × 10^9/litre
iv. Erythrocyte count	4.2–5.9 million/mm^3	4.2–5.9 × 10^{12}/litre
v. Mean corpuscular volume (MCV)	86–98 μm^3/cell	86–96 fl
vi. Mean corpuscular hemoglobin (MCH)	27–32 pg/RBC	1.7–2.0 pg/cell
vii. Mean corpuscular hemoglobin concentration (MCHC)	32–36%	0.32–0.36
d. Erythrocyte sedimentation rate	Male: 1–13 mm/hour Female: 1–20 mm/hour	Male: 1–13 mm/hour Female: 1–20 mm/hour
e. Ferritin (serum)		
Iron deficiency	0–12 ng/ml (13–20 ng/ml, borderline)	0–4.8 nmol/litre (5.2–8 nmol/litre, borderline)
Iron excess	> 400 ng/ml	> 160 nmol/litre
f. Folic acid (normal)	> 3.3 ng/ml	> 7.3 nmol/litre
g. Leucocyte alkaline phosphatase:		
Qualitative method	Male: 33–188 U Female (off contraceptive pill): 30–160 U	33–188 U 30–160 U
h. Platelet count	150,000–350,000/mm^3	150–350 × 10^9/litre
i. Reticulocyte count	0.5–2.5% red cells	0.005–0.025
j. Vitamin B_{12}	205–876 pg/ml	150–674 pmol/litre

5. Cerebrospinal fluid value

Determination	*Reference range*	
	Conventional	*SI*
1. Cell count	0–5 mononuclear cells	—
2. Chloride	120–130 mEq/litre	120–130 mmol/litre
3. Albumin	Mean: 29.5 mg/100 ml ± 2SD: 11–48 mg/100 ml	0.295 g/litre ±2 SD: 0.11–0.48
4. IgG	Mean: 4.3 mg/100 ml ± 2SD: 0–8.6 mg/100 ml	0.043 g/litre ±2 SD: 0–0.086
5. Glucose	50–75 mg/100ml	2.8–4.2 mmol/litre
6. Pressure (initial)	70–180 mm of water	70–180 arb. unit
7. Protein		
a. Lumbar	15–45 mg/100 ml	0.15–0.45 g/litre
b. Cisternal	15–25 mg/100 ml	0.15–0.25 g/litre
c. Ventricular	5–15 mg/100 ml	0.05–0.15 g/litre

6. Miscellaneous values

1. pH (urine)	5–7	5–7
2. Complement, total hemolytic	150–250 U/ml	—
3. C3	Range 83–177 mg/100 ml	0.83–1.77 g/litre
4. C4	Range 15–45 mg/100 ml	0.15–0.45 g/litre
5. Immunoglobulins:		
IgG	639–1349 mg/100 ml	6.39–13.49 g/litre
IgA	70–312 mg/100 ml	0.7–3.12 g/litre
IgM	86–352 mg/100 ml	0.86–3.52 g/litre
Viscosity	1.4–1.8 relative viscosity units	—
6. Stool fat	Less than 6g in 24 hours or less than 6% of measured fat intake in 3-day period	< 6 g/day
7. Synovial fluid: Glucose	Not less than 20 mg/100 ml lower than simultaneously drawn blood sugar	(see blood glucose)
8. D-xylose absorption	4–5 g/5 hours in urine; 30 mg per 100 ml in blood 2 hours after ingestion of 25 g of D-xylose	26–33 mmol/day 2.0 mmol/litre

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ISBN 81-250-1559-0

Orient Longman

R S Vasan, Sudha Seshadri *Textbook of Medicine*